Prevention of Thromboembolic Complications in Atrial Fibrillation

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Nov 5th, 2016

Disclosures

- None

Prevention of Thromboembolic Complications in Atrial Fibrillation (Ten things to consider)

- ***You must know the*** *CHA_2DS_2-VASc score*

Why you must know the CHA_2DS_2VASc Score

ACC/AHA Performance Measures

2016 ACC/AHA Clinical Performance and Quality Measures for Adults With Atrial Fibrillation or Atrial Flutter

A Report of the American College of Cardiology/American Heart Association Task Force on Performance Measures

Developed in Collaboration With the Heart Rhythm Society

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§American College of Cardiology Representative.

This document underwent a 14-day peer review between October 6, 2015, and October 20, 2015, and a 30-day public comment period between October 6, 2015, and November 4, 2015.

This document was approved by the American College of Cardiology Board of Trustees on January 20, 2016, and the Executive Committee on February 8, 2016; by the American Heart Association Science Advisory and Coordinating Committee on January 21, 2016, and the Executive Committee on March 2, 2016; and by the Heart Rhythm Society on February 25, 2016.

The Comprehensive RWI Data Supplement table is available with this article at http://circoutcomes.ahajournals.org/lookup/suppl/doi:10.1161/HCQ.0000000000000018/-/DC1.

The American Heart Association requests that this document be cited as follows: Heidenreich PA, Solis P, Estes NAM 3rd, Fonarow GC, Jurgens CY, Marine JE, McManus DD, McNamara RL. 2016 ACC/AHA clinical performance and quality measures for adults with atrial fibrillation or atrial flutter: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures. *Circ Cardiovasc Qual Outcomes.* 2016;9:443–488. DOI: 10.1161/HCQ.0000000000000018.

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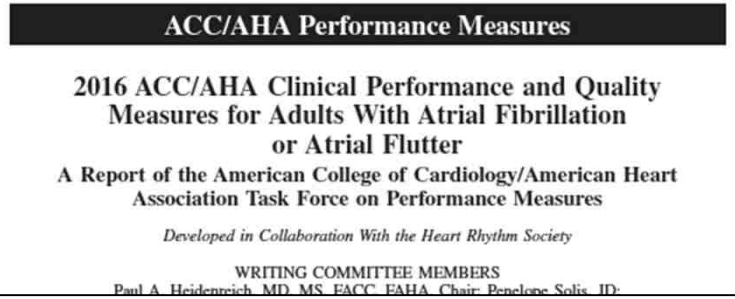
Circ Cardiovasc Qual Outcomes. 2016;9:443-488

Why you must know the CHA_2DS_2VASc Score



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Paul A. Heidenreich, MD, MS, FACC, FAHA, Chair; Penelope Solis, JD;

?The writing committee has worked to create **a comprehensive list of measures** that can be **used for patients with AF**. This set includes ***21 new measures***, of which ***3 are inpatient performance measures*** and 18 are quality measures (10 inpatient, 8 outpatient). Table 5 includes a list of the measures with information on the care setting and a brief rationale."

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Circ Cardiovasc Qual Outcomes. 2016;9:443-488

ACC/AHA Performance Measures

Table 1. 2016 ACC/AHA Atrial Fibrillation Clinical Performance and Quality Measures

No.	Measure Title	Care Setting	Measure Domain
Performance Measures			
PM-1	CHA_2DS_2-VASc Risk Score Documented Prior to Discharge	Inpatient	Effective Clinical Care
PM-2	Anticoagulation Prescribed Prior to Discharge	Inpatient	Effective Clinical Care
PM-3	PT/INR Planned Follow-Up Documented Prior to Discharge for Warfarin Treatment	Inpatient	Effective Clinical Care
PM-4	CHA_2DS_2-VASc Risk Score Documented	Outpatient	Effective Clinical Care
PM-5	Anticoagulation Prescribed	Outpatient	Effective Clinical Care
PM-6	Monthly INR for Warfarin Treatment	Outpatient	Effective Clinical Care
Quality Measures			
QM-1	Beta Blocker Prescribed Prior to Discharge (When LVEF ≤40)	Inpatient	Effective Clinical Care
QM-2	ACEI or Angiotensin-Receptor Blocker Prescribed Prior to Discharge (When LVEF ≤40)	Inpatient	Effective Clinical Care
QM-3	Inappropriate Prescription of Antiarrhythmic Drugs Prior to Discharge to Patients With Permanent	Inpatient	Patient Safety
QM-9	Patients Who Underwent Atrial Fibrillation Catheter Ablation Who Were Not Treated With Anticoagulation Therapy During or After a Procedure	Inpatient	Patient Safety
QM-10	Shared Decision Making Between Physician and Patient in Anticoagulation Prescription Prior to Discharge	Inpatient	Communication and Care Coordination
QM-11	Beta Blocker Prescribed (When LVEF ≤40)	Outpatient	Effective Clinical Care
QM-12	Inappropriate Prescription of Antiarrhythmic Drugs to Patients With Permanent Atrial Fibrillation for Rhythm Control	Outpatient	Patient Safety
QM-13	Inappropriate Prescription of Dofetilide or Sotalol in Patients With Atrial Fibrillation and End-Stage Kidney Disease or on Dialysis	Outpatient	Patient Safety
QM-14	Inappropriate Prescription of a Direct Thrombin or Factor Xa Inhibitor in Patients With Atrial Fibrillation With Mechanical Heart Valve	Outpatient	Patient Safety
QM-15	Inappropriate Prescription of a Direct Thrombin or Factor Xa Inhibitor (Rivaroxaban or Edoxaban) in Patients With Atrial Fibrillation and End-Stage Kidney Disease or on Dialysis	Outpatient	Patient Safety
QM-16	Inappropriate Prescription of Antiplatelet and Oral Anticoagulation Therapy for Patients Who Do Not Have Coronary Artery Disease and/or Vascular Disease	Outpatient	Patient Safety
QM-17	Inappropriate Prescription of Nondihydropyridine Calcium Channel Antagonist in Patients With Reduced Ejection Fraction Heart Failure	Outpatient	Patient Safety
QM-18	Shared Decision Making Between Physician and Patient in Anticoagulation Prescription	Outpatient	Communication and Care Coordination

ACC indicates American College of Cardiology; ACE, angiotensin-converting enzyme; ACEI, angiotensin-converting enzyme inhibitor; AHA, American Heart Association; ARB, angiotensin receptor blocker; INR, International Normalized Ratio; LVEF, left ventricular ejection fraction; PM, performance measure; PT, prothrombin time; and QM, quality measure.

The ACC/AHA **Task Force** on Performance Measures ***distinguishes quality measures from performance measures***. Quality measures are metrics that *may* be useful for local quality improvement but are not yet appropriate for ***public reporting or pay-for-performance programs*** (ie, contexts in which performance measures are used).

Circ Cardiovasc Qual Outcomes. 2016;9:443-488

ACC/AHA Performance Measures

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PM-6	Monthly INR for Warfarin Treatment	Outpatient	Effective Clinical Care

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What is the CHA_2DS_2VASc Score?

THE WALL STREET JOURNAL.

THE NUMBERS
Turns Out, Counting on Your Fingers Makes You Smarter

Judge Orders Ex-NSA Contractor to Remain in Custody

Some at Facebook Wanted to Remove Trump's Posts as Hate Speech ...

Some Republican Lawmakers Sour on Death Penalty

Black W… Fastest … in More Years

U.S. | THE NUMBERS

Turns Out, Counting on Your Fingers Makes You Smarter

Children who have better perception of their hands tend to be more skilled at math, research shows.

Recent research shows that finger recognition is correlated with math skills. *PHOTO: GETTY IMAGES*

Wall Street Journal; Oct 21st, 2016

Where did the CHA_2DS_2 VASc score come from?

AHA/ACC/HRS Practice Guideline

2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society

Developed in Collaboration With the Society of Thoracic Surgeons

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*Writing committee members are required to recuse themselves from voting on sections to which their specific relationships with industry and other entities may apply; see Appendix 1 for recusal information.

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‖Society of Thoracic Surgeons Representative.

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#Former Task Force member; current member during the writing effort.

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The online-only Comprehensive Relationships Data Supplement is available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000041/-/DC1.

The online-only Data Supplement files are available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000041/-/DC2.

The American Heart Association requests that this document be cited as follows: January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *Circulation* 2014;130:e199–e267.

This article is copublished in the *Journal of the American College of Cardiology*.

(*Circulation*. 2014;130:e199–e267.)

Circulation is available at http://circ.ahajournals.org DOI: 10.1161/CIR.0000000000000041

Table 5. Selected Risk Factors and Biomarkers for AF

Clinical Risk Factors	References
Increasing age	139
Hypertension	139
Diabetes mellitus	139
MI	139
VHD	139
HF	38,139
Obesity	140–142
Obstructive sleep apnea	142
Cardiothoracic surgery	137
Smoking	143
Exercise	144–146
Alcohol use	147–149
Hyperthyroidism	150–152
Increased pulse pressure	153
European ancestry	154
Family history	155
Genetic variants	156–159
ECG	
LVH	35
Echocardiographic	
LA enlargement	35,160
Decreased LV fractional shortening	35
Increased LV wall thickness	35
Biomarkers	
Increased CRP	86,161
Increased BNP	162,163

AF indicates atrial fibrillation; BNP, B-type natriuretic peptide; CRP, C-reactive protein; ECG, electrocardiographic; HF, heart failure; LA, left atrial; LV, left ventricular; LVH, left ventricular hypertrophy; MI, myocardial infarction; and VHD, valvular heart disease.

Circulation 2014;130:e199-e267

2014 AHA/ACC/HRS G
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A Report of the American
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This article is copublished in the *Journal of the American College*

(*Circulation*. 2014;130:e199-e267.)

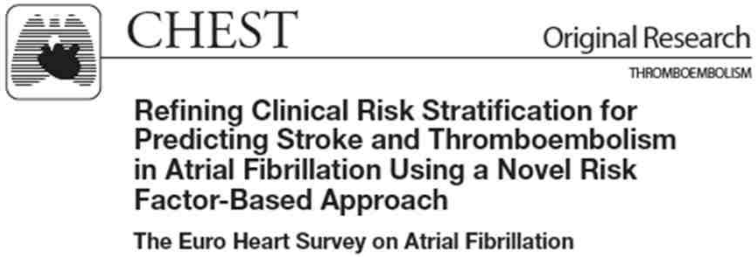
***Circulation* is available at http://circ.ahajournals.org**

Table 7. Comparison of the $CHADS_2$ and CHA_2DS_2-VASc Risk Stratification Scores for Subjects With Nonvalvular AF

Definition and Scores for $CHADS_2$ and CHA_2DS_2-VASc		Stroke Risk Stratification With the $CHADS_2$ and CHA_2DS_2-VASc Scores	
	Score		Adjusted Stroke Rate (% per y)
$CHADS_2$		$CHADS_2$*	
Congestive HF	1	0	1.9
Hypertension	1	1	2.8
Age ≥75 y	1	2	4.0
Diabetes mellitus	1	3	5.9
Stroke/TIA/TE	2	4	8.5
Maximum score	6	5	12.5
		6	18.2
CHA_2DS_2-VASc		CHA_2DS_2-VASc†	
Congestive HF	1	0	0
Hypertension	1	1	1.3
Age ≥75 y	2	2	2.2
Diabetes mellitus	1	3	3.2
Stroke/TIA/TE	2	4	4.0
Vascular disease (prior MI, PAD, or aortic plaque)	1	5	6.7
Age 65–74 y	1	6	9.8
Sex category (ie, female sex)	1	7	9.6
Maximum score	9	8	6.7
		9	15.20

Circulation 2014;130:e199-e267

Where did the CHA_2DS_2 VASc score come from?



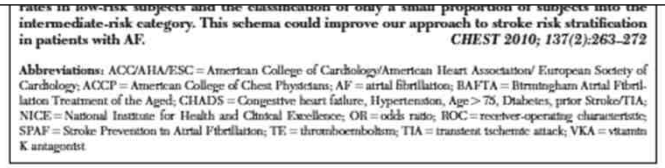
CHEST Original Research

THROMBOEMBOLISM

Refining Clinical Risk Stratification for Predicting Stroke and Thromboembolism in Atrial Fibrillation Using a Novel Risk Factor-Based Approach

The Euro Heart Survey on Atrial Fibrillation

Current treatment guidelines recommend VKA for high-risk subjects and (usually) aspirin for low risk subjects, but **for intermediate risk, many guidelines state "either warfarin or aspirin" can be used**. The latter can sometimes **cause uncertainty for clinicians managing such patients, especially if a large proportion of a particular cohort of patients** with AF are classified into this intermediate-risk category. **This "either warfarin or aspirin" recommendation is also sometimes used as an excuse not to prescribe warfarin in intermediate-risk patients.**



rates in low-risk subjects and the classification of only a small proportion of subjects into the intermediate-risk category. This schema could improve our approach to stroke risk stratification in patients with AF. *CHEST 2010; 137(2):263–272*

Abbreviations: ACC/AHA/ESC = American College of Cardiology/American Heart Association/ European Society of Cardiology; ACCP = American College of Chest Physicians; AF = atrial fibrillation; BAFTA = Birmingham Atrial Fibrillation Treatment of the Aged; CHADS = Congestive heart failure, Hypertension, Age > 75, Diabetes, prior Stroke/TIA; NICE = National Institute for Health and Clinical Excellence; OR = odds ratio; ROC = receiver-operating characteristic; SPAF = Stroke Prevention in Atrial Fibrillation; TE = thromboembolism; TIA = transient ischemic attack; VKA = vitamin K antagonist

Atrial fibrillation (AF) is the most common sustained cardiac rhythm disorder, which is associated with a substantial risk of mortality and morbidity from stroke and thromboembolism (TE). A substantial evidence base is in favor of anticoagulation with the vitamin K antagonists (VKAs, eg, warfarin), which reduce this risk by two-thirds, whereas antiplatelet therapy decreases stroke risk only by 22%.[1] VKAs are

CHEST 2010; 137(2):263–272

Where did the CHA_2DS_2 VASc score come from?

CHEST Original Research
THROMBOEMBOLISM

Refining Clinical Risk Stratification for Predicting Stroke and Thromboembolism in Atrial Fibrillation Using a Novel Risk Factor-Based Approach

The Euro Heart Survey on Atrial Fibrillation

As our analysis (and that of others) has shown, the **classic CHADS 2 version generated a large intermediate risk group (60%) for whom it is unclear which treatment (warfarin or aspirin) to apply…. but with the addition of vascular disease, female gender, or age 65 to 74 years to a risk factor-based schema there was further refinement of TE risk stratification for AF.**

(C-statistic, 0.606) than $CHADS_2$. However, those classified as low risk by the Birmingham 2009 and NICE schema were truly low risk with no TE events recorded, whereas TE events occurred in 1.4% of low-risk $CHADS_2$ subjects. When expressed as a scoring system, the Birmingham 2009 schema (CHA_2DS_2-VASc acronym) showed an increase in TE rate with increasing scores (*P* value for trend = .003).

Conclusion: Our novel, simple stroke risk stratification schema, based on a risk factor approach, provides some improvement in predictive value for TE over the $CHADS_2$ schema, with low event rates in low-risk subjects and the classification of only a small proportion of subjects into the intermediate-risk category. This schema could improve our approach to stroke risk stratification in patients with AF.

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Abbreviations: ACC/AHA/ESC = American College of Cardiology/American Heart Association/ European Society of Cardiology; ACCP = American College of Chest Physicians; AF = atrial fibrillation; BAFTA = Birmingham Atrial Fibrillation Treatment of the Aged; CHADS = Congestive heart failure, Hypertension, Age > 75, Diabetes, prior Stroke/TIA; NICE = National Institute for Health and Clinical Excellence; OR = odds ratio; ROC = receiver-operating characteristic; SPAF = Stroke Prevention in Atrial Fibrillation; TE = thromboembolism; TIA = transient ischemic attack; VKA = vitamin K antagonist

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Underuse of OACs in Afib

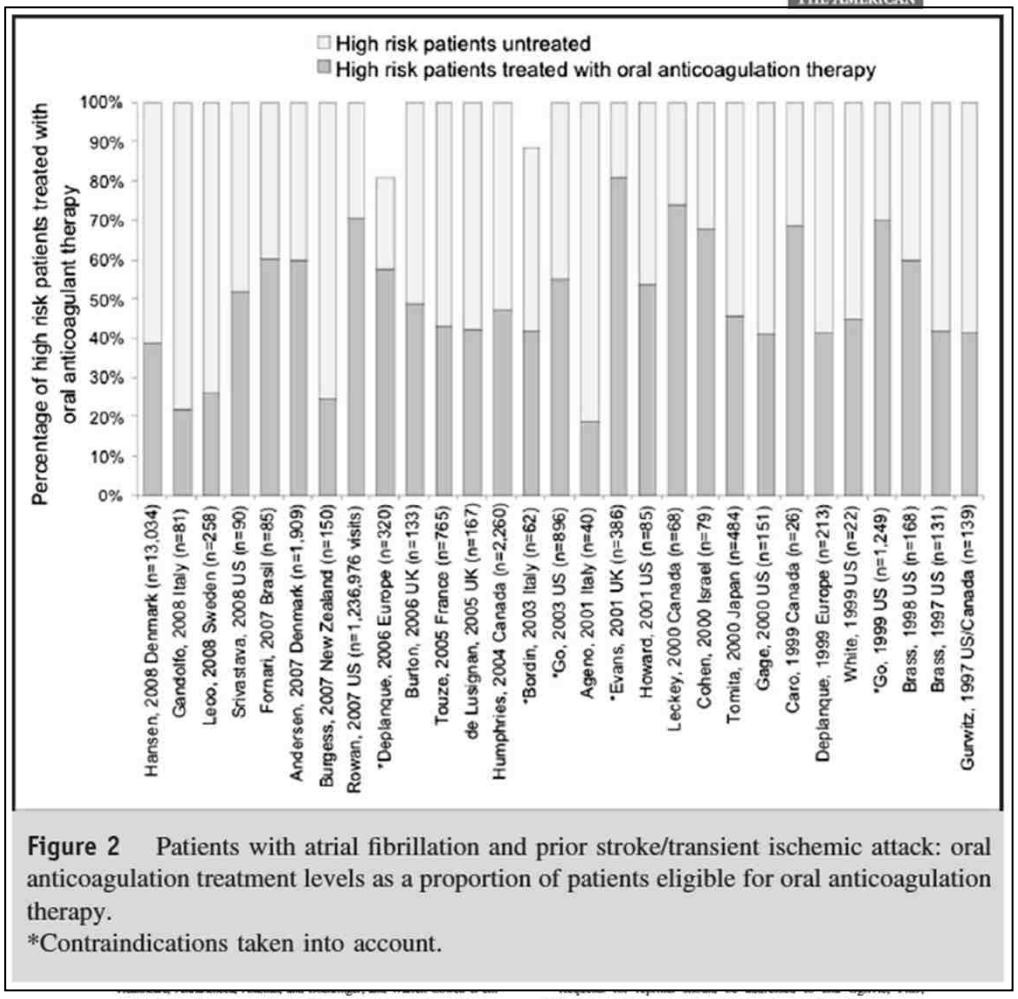

Figure 2 Patients with atrial fibrillation and prior stroke/transient ischemic attack: oral anticoagulation treatment levels as a proportion of patients eligible for oral anticoagulation therapy.
*Contraindications taken into account.

ployed by Bayer Healthcare, UK. The other authors have no conflict of interest.
Authorship: All authors had full access to data for this study and participated in writing and review of the manuscript.

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The American Journal of Medicine (2010) 123, 638-645

Why is it important to risk stratify patients for stroke?

CLINICIAN UPDATE

Use of the CHA_2DS_2-VASc and HAS-BLED Scores to Aid Decision Making for Thromboprophylaxis in Nonvalvular Atrial Fibrillation

Deirdre A. Lane, PhD; Gregory Y.H. Lip, MD

Even patients classified as low risk by CHADS2 in its original validation study have a stroke rate of 1.9%/y, which is close to the criterion of a cardiovascular event rate of 20% over 10 years for primary prevention strategies (eg, the use of statins).

patient clinic 4 weeks later with a history of intermittent palpitations. Her average clinic blood pressure was 140/85 mm Hg, and the 30-day cardiac loop monitor demonstrated AF, which coincided with diary entries of symptoms of palpitations. What is the most appropriate stroke prophylaxis for this patient, given her new-onset AF?

AF increases the risk of stroke 5-fold, and anticoagulant therapy reduces the risk of stroke and all-cause mortality.[1,2] Consequently, clinical guidelines recommend stroke thromboprophylaxis among AF patients unless they are at low risk; low-risk patients are defined as those with age <65 years and lone AF.[1,2] Indeed, the risk of stroke among patients with

categorized AF patients into low, moderate, and high risk. Traditionally, guidelines have recommended aspirin or antiplatelet therapy for those at low risk of stroke and oral anticoagulation (OAC) for those at high risk, whereas individuals at moderate risk have the option of receiving either aspirin or oral anticoagulation. To determine the most appropriate antithrombotic therapy for each patient, the individual risk of stroke should be assessed.

Systematic reviews[3–5] demonstrate that the main risk factors for stroke in patients with AF are previous stroke or transient ischemic attack, increasing age, hypertension, heart failure, and diabetes mellitus (Table 1). The widely used $CHADS_2$ score[6] (Congestive

Female sex
Vascular disease
Coronary or peripheral artery disease

Heart Failure, Hypertension, Age ≥75 Years, Diabetes Mellitus [1 point for presence of each], and Stroke/TIA [2 points]; scores range from 0 to 6) was derived from the risk factors obtained from the original (now historical) data sets from the AF Investigators and the Stroke Prevention in AF 1 trial. Of note, the historical trials randomized <10% of the patients who were screened, and many risk factors were inconsistently defined or systematically recorded.

Over the last decade, major developments have led to significant

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(*Circulation*. 2012;126:860-865.)

Circulation is available at http://circ.ahajournals.org
DOI: 10.1161/CIRCULATIONAHA.111.060061

Circulation. 2012;126:860-865

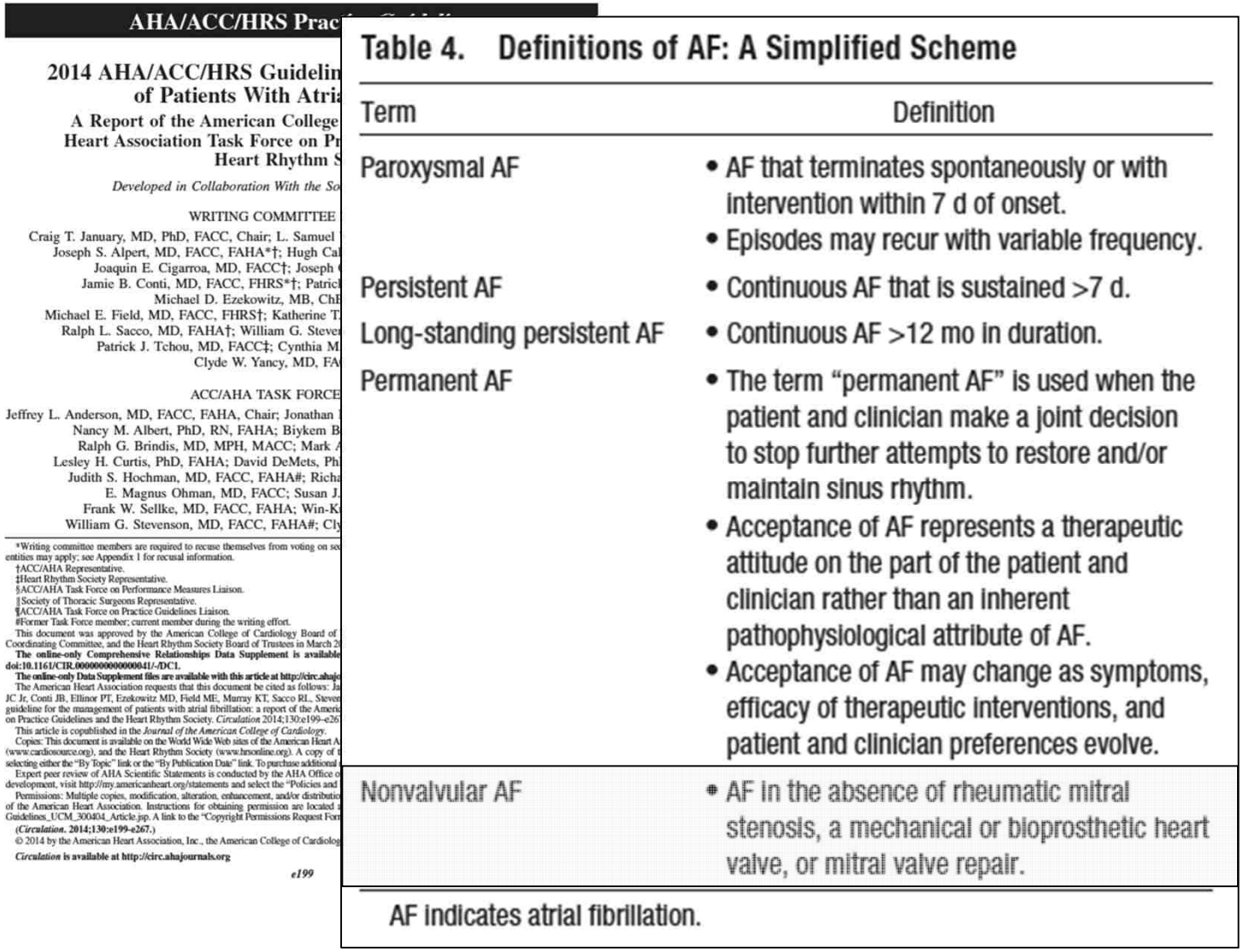
Removing the barriers to OAC in patients with afib and aflutter

- **Identifying the barriers**
  - **Stratification scheme too complex (low, med, high)**
    - **Solution: make scheme ”low and high”**
  - **Risk algorithm too complex**
    - **Solution: easily identified factors**
  - **Risk algorithm fails to identify “truly low” risk patients who do not need OAC**
    - **Solution: refine algorithm**
  - ***Substitute questionably effective treatments with treatments known/proven to be effective***
    - ***Solution: eliminate ASA as treatment; thus, treatment choice becomes “nothing” for AF patient with NO risk factors other than “female” or OAC for everyone else.***

Prevention of Thromboembolic Complications in Atrial Fibrillation (Ten things to consider)

- **You must know the** CHA_2DS_2-VASc score
- *What does the term "non valvular atrial fibrillation mean"?*

What is “non-valvular”? (2014)



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This document was approved by the American College of Cardiology Board of
Coordinating Committee, and the Heart Rhythm Society Board of Trustees in March 2
The online-only Comprehensive Relationships Data Supplement is available
doi:10.1161/CIR.0000000000000041/-/DC1.
The online-only Data Supplement files are available with this article at http://circ.ahaj
The American Heart Association requests that this document be cited as follows: Ja
JC Jr, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Steven
guideline for the management of patients with atrial fibrillation: a report of the Americ
on Practice Guidelines and the Heart Rhythm Society. *Circulation* 2014;130:e199–e26
This article is copublished in the *Journal of the American College of Cardiology*.
Copies: This document is available on the World Wide Web sites of the American Heart A
(www.cardiosource.org), and the Heart Rhythm Society (www.hrsonline.org). A copy of
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(*Circulation*. 2014;130:e199-e267.)
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***Circulation* is available at http://circ.ahajournals.org**

e199

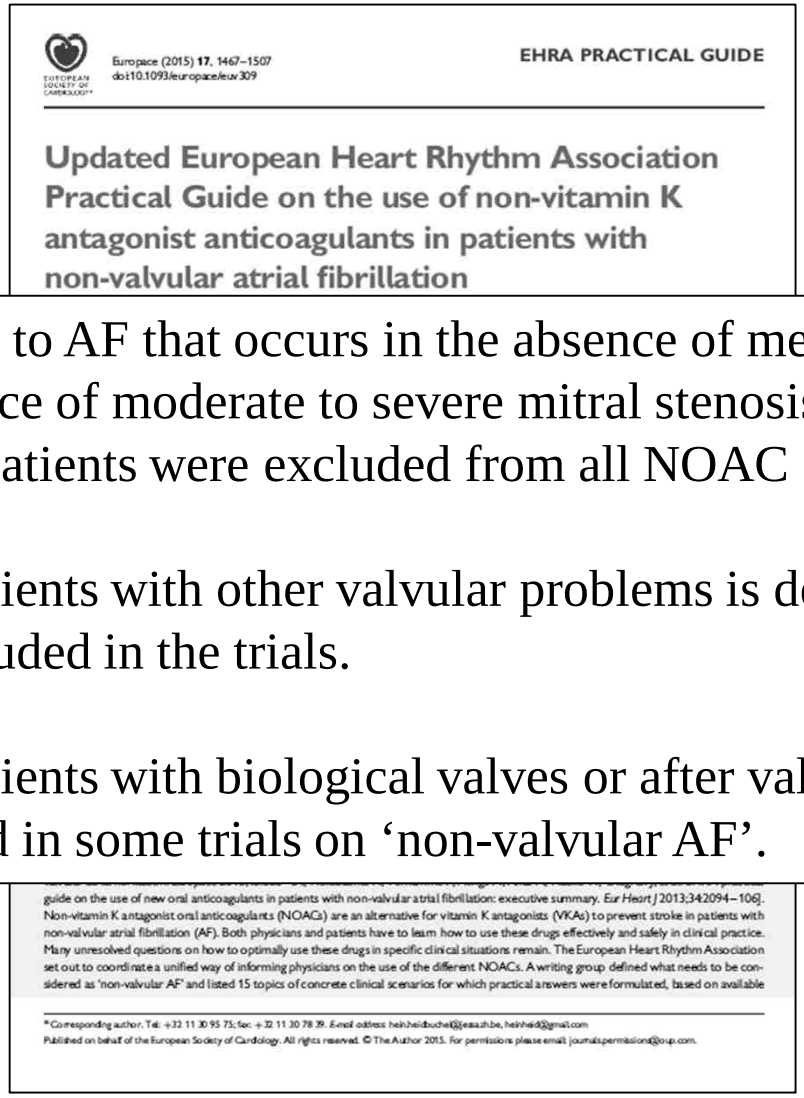
Table 4. Definitions of AF: A Simplified Scheme

Term	Definition
Paroxysmal AF	• AF that terminates spontaneously or with intervention within 7 d of onset. • Episodes may recur with variable frequency.
Persistent AF	• Continuous AF that is sustained >7 d.
Long-standing persistent AF	• Continuous AF >12 mo in duration.
Permanent AF	• The term “permanent AF” is used when the patient and clinician make a joint decision to stop further attempts to restore and/or maintain sinus rhythm. • Acceptance of AF represents a therapeutic attitude on the part of the patient and clinician rather than an inherent pathophysiological attribute of AF. • Acceptance of AF may change as symptoms, efficacy of therapeutic interventions, and patient and clinician preferences evolve.
Nonvalvular AF	• AF in the absence of rheumatic mitral stenosis, a mechanical or bioprosthetic heart valve, or mitral valve repair.

AF indicates atrial fibrillation.

Circulation 2014;130:e199-e267

What is “non-valvular”? (2015)



Europace (2015) 17, 1467–1507 doi:10.1093/europace/euv309

EHRA PRACTICAL GUIDE

Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation

guide on the use of new oral anticoagulants in patients with non-valvular atrial fibrillation: executive summary. *Eur Heart J* 2013;34:2094–106].
Non-vitamin K antagonist oral anticoagulants (NOACs) are an alternative for vitamin K antagonists (VKAs) to prevent stroke in patients with non-valvular atrial fibrillation (AF). Both physicians and patients have to learn how to use these drugs effectively and safely in clinical practice. Many unresolved questions on how to optimally use these drugs in specific clinical situations remain. The European Heart Rhythm Association set out to coordinate a unified way of informing physicians on the use of the different NOACs. A writing group defined what needs to be considered as 'non-valvular AF' and listed 15 topics of concrete clinical scenarios for which practical answers were formulated, based on available

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- Non-valvular AF refers to AF that occurs in the absence of mechanical prosthetic heart valves and in the absence of moderate to severe mitral stenosis (usually of rheumatic origin). Both types of patients were excluded from all NOAC trials.
- Atrial fibrillation in patients with other valvular problems is defined as ‘non-valvular’ and such patients were included in the trials.
- Atrial fibrillation in patients with biological valves or after valve repair constitute a grey area, and were included in some trials on ‘non-valvular AF’.

Europace (2015) 17, 1467–1507

Johnson & Johnson Pharmaceutical Research & Development*

Clinical Protocol

A Prospective, Randomized, Double-Blind, Double-Dummy, Parallel-Group, Multicenter, Event-Driven, Non-inferiority Study Comparing the Efficacy and Safety of Once-Daily Oral Rivaroxaban (BAY 59-7939) With Adjusted-Dose Oral Warfarin for the Prevention of Stroke and Non-Central Nervous System Systemic Embolism in Subjects With Non-Valvular Atrial Fibrillation

Protocol 39039039AFL3001; Phase 3
(EudraCT number 2006-004595-13)
BAY59-7939/11630
JNJ39039039 (rivaroxaban, BAY 59-7939)

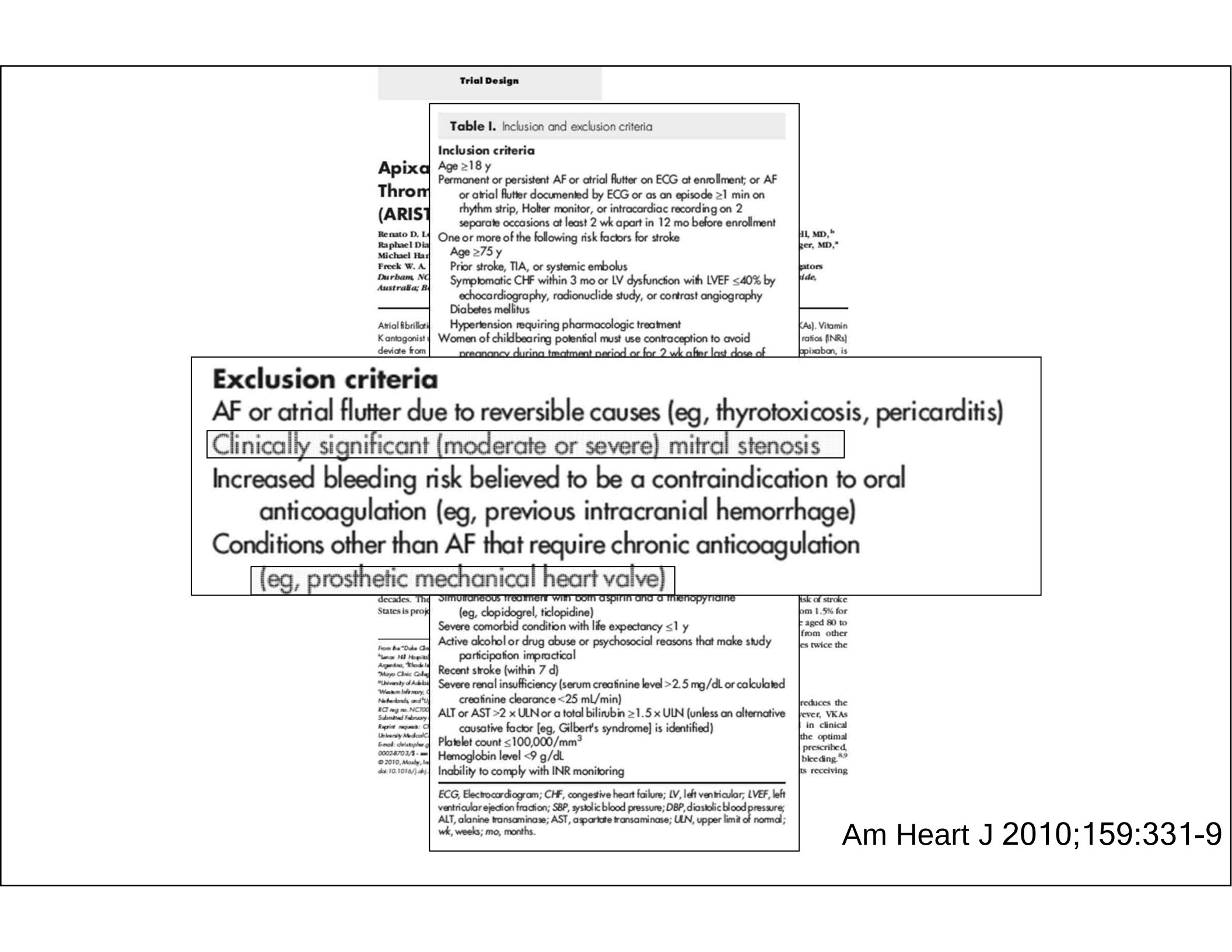
Amendment INT-2

*Rivaroxaban (BAY-59-7939, JNJ-39039039) is being co-developed under a collaboration and license

5.3. Exclusion Criteria	• Prosthetic heart valve **(annuloplasty with or without prosthetic ring, commissurotomy and/or valvuloplasty are permitted)**	Specification of permitted conditions.

Issue/Report Date: 13 FEBRUARY 2009
Prepared by: Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Department: Drug Development
Document No.: EDMS-PSDB-5429061:5.0

Protocol for: Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365:883-91. DOI: 10.1056/NEJMoa1009638.



Trial Design

Table I. Inclusion and exclusion criteria

Inclusion criteria

Age ≥18 y

Permanent or persistent AF or atrial flutter on ECG at enrollment; or AF or atrial flutter documented by ECG or as an episode ≥1 min on rhythm strip, Holter monitor, or intracardiac recording on 2 separate occasions at least 2 wk apart in 12 mo before enrollment

One or more of the following risk factors for stroke

- Age ≥75 y
- Prior stroke, TIA, or systemic embolus
- Symptomatic CHF within 3 mo or LV dysfunction with LVEF ≤40% by echocardiography, radionuclide study, or contrast angiography
- Diabetes mellitus
- Hypertension requiring pharmacologic treatment

Women of childbearing potential must use contraception to avoid pregnancy during treatment period or for 2 wk after last dose of

Exclusion criteria

AF or atrial flutter due to reversible causes (eg, thyrotoxicosis, pericarditis)

Clinically significant (moderate or severe) mitral stenosis

Increased bleeding risk believed to be a contraindication to oral anticoagulation (eg, previous intracranial hemorrhage)

Conditions other than AF that require chronic anticoagulation (eg, prosthetic mechanical heart valve)

Simultaneous treatment with both aspirin and a thienopyridine (eg, clopidogrel, ticlopidine)

Severe comorbid condition with life expectancy ≤1 y

Active alcohol or drug abuse or psychosocial reasons that make study participation impractical

Recent stroke (within 7 d)

Severe renal insufficiency (serum creatinine level >2.5 mg/dL or calculated creatinine clearance <25 mL/min)

ALT or AST >2 × ULN or a total bilirubin ≥1.5 × ULN (unless an alternative causative factor [eg, Gilbert's syndrome] is identified)

Platelet count ≤100,000/mm^3

Hemoglobin level <9 g/dL

Inability to comply with INR monitoring

ECG, Electrocardiogram; *CHF*, congestive heart failure; *LV*, left ventricular; *LVEF*, left ventricular ejection fraction; *SBP*, systolic blood pressure; *DBP*, diastolic blood pressure; ALT, alanine transaminase; AST, aspartate transaminase; *ULN*, upper limit of normal; *wk*, weeks; *mo*, months.

Am Heart J 2010;159:331-9

What is “non-valvular”? (2015)

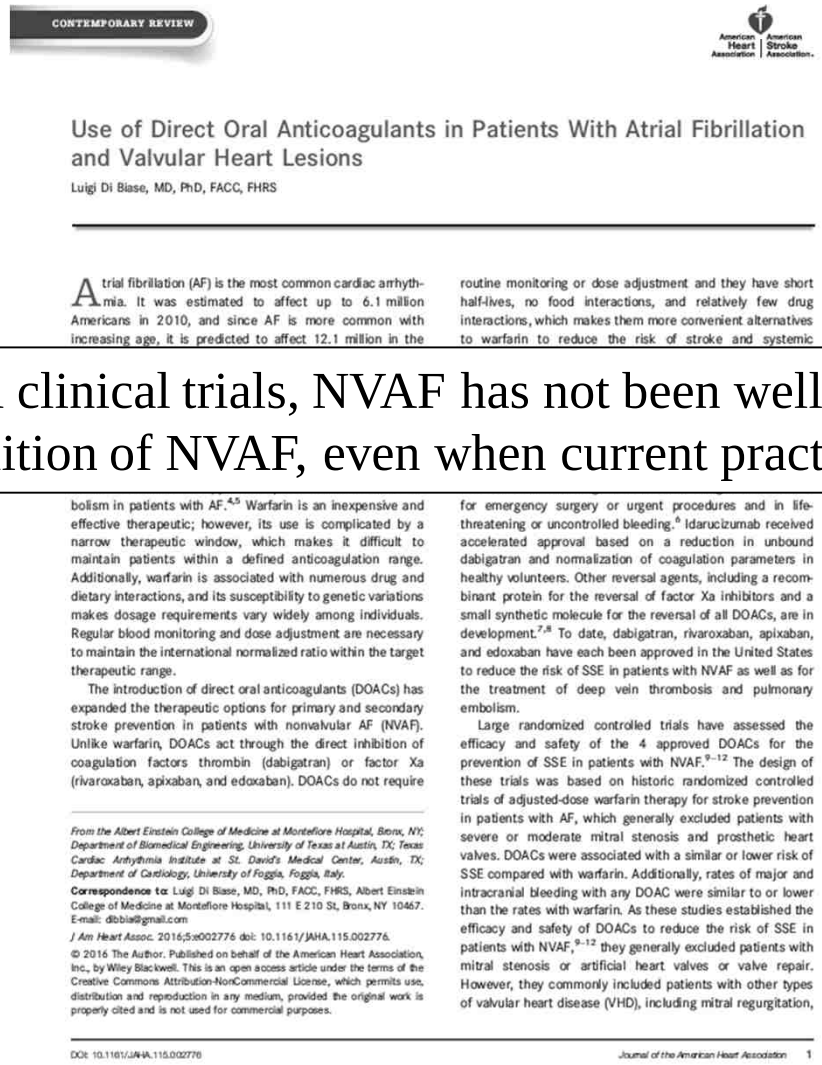
Table 1 Valvular indications and contraindications for NOAC therapy in AF patients

	Eligible	Contra-indicated
Mechanical prosthetic valve		✓
Moderate to severe mitral stenosis (usually of rheumatic origin)		✓
Mild to moderate other native valvular disease	✓	
Severe aortic stenosis	✓ Limited data. Most will undergo intervention	
Bioprosthetic valve[a]	✓ (except for the first 3 months post-operatively)	
Mitral valve repair[a]	✓ (except for the first 3–6 months post-operatively)	
PTAV and TAVI	✓ (but no prospective data; may require combination with single or double antiplatelets: consider bleeding risk)	
Hypertrophic cardiomyopathy	✓ (but no prospective data)	

PTAV, percutaneous transluminal aortic valvuloplasty; TAVI, transcatheter aortic valve implantation.
[a]American guidelines do not recommend NOAC in patients with biological heart valves or after valve repair.[8]

Europace (2015) 17, 1467–1507

What is “non-valvular”? (Feb 2016)



CONTEMPORARY REVIEW

American Heart Association | American Stroke Association

Use of Direct Oral Anticoagulants in Patients With Atrial Fibrillation and Valvular Heart Lesions

Luigi Di Biase, MD, PhD, FACC, FHRS

Atrial fibrillation (AF) is the most common cardiac arrhythmia. It was estimated to affect up to 6.1 million Americans in 2010, and since AF is more common with increasing age, it is predicted to affect 12.1 million in the

bolism in patients with AF.[4,5] Warfarin is an inexpensive and effective therapeutic; however, its use is complicated by a narrow therapeutic window, which makes it difficult to maintain patients within a defined anticoagulation range. Additionally, warfarin is associated with numerous drug and dietary interactions, and its susceptibility to genetic variations makes dosage requirements vary widely among individuals. Regular blood monitoring and dose adjustment are necessary to maintain the international normalized ratio within the target therapeutic range.

The introduction of direct oral anticoagulants (DOACs) has expanded the therapeutic options for primary and secondary stroke prevention in patients with nonvalvular AF (NVAF). Unlike warfarin, DOACs act through the direct inhibition of coagulation factors thrombin (dabigatran) or factor Xa (rivaroxaban, apixaban, and edoxaban). DOACs do not require routine monitoring or dose adjustment and they have short half-lives, no food interactions, and relatively few drug interactions, which makes them more convenient alternatives to warfarin to reduce the risk of stroke and systemic

for emergency surgery or urgent procedures and in life-threatening or uncontrolled bleeding.[6] Idarucizumab received accelerated approval based on a reduction in unbound dabigatran and normalization of coagulation parameters in healthy volunteers. Other reversal agents, including a recombinant protein for the reversal of factor Xa inhibitors and a small synthetic molecule for the reversal of all DOACs, are in development.[7,8] To date, dabigatran, rivaroxaban, apixaban, and edoxaban have each been approved in the United States to reduce the risk of SSE in patients with NVAF as well as for the treatment of deep vein thrombosis and pulmonary embolism.

Large randomized controlled trials have assessed the efficacy and safety of the 4 approved DOACs for the prevention of SSE in patients with NVAF.[9–12] The design of these trials was based on historic randomized controlled trials of adjusted-dose warfarin therapy for stroke prevention in patients with AF, which generally excluded patients with severe or moderate mitral stenosis and prosthetic heart valves. DOACs were associated with a similar or lower risk of SSE compared with warfarin. Additionally, rates of major and intracranial bleeding with any DOAC were similar to or lower than the rates with warfarin. As these studies established the efficacy and safety of DOACs to reduce the risk of SSE in patients with NVAF,[9–12] they generally excluded patients with mitral stenosis or artificial heart valves or valve repair. However, they commonly included patients with other types of valvular heart disease (VHD), including mitral regurgitation,

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Correspondence to: Luigi Di Biase, MD, PhD, FACC, FHRS, Albert Einstein College of Medicine at Montefiore Hospital, 111 E 210 St, Bronx, NY 10467. E-mail: dibbia@gmail.com

J Am Heart Assoc. 2016;5:e002776 doi: 10.1161/JAHA.115.002776.

“Outside of the pivotal clinical trials, NVAF has not been well defined. There is currently no consensus on the definition of NVAF, even when current practice guidelines are examined.”

J Am Heart Assoc. 2016;5:e002776

What is “non-valvular”? (July 2016)

ACC/AHA Performance Measures

2016 ACC/AHA Clinical Performance and Quality Measures for Adults With Atrial Fibrillation or Atrial Flutter

A Report of the American College of Cardiology/American Heart

QM-5	Inpatient	Inappropriate Prescription of a Direct Thrombin or Factor Xa Inhibitor Discharge in Patients With Atrial Fibrillation With a Mechanical Heart Valve	According to the 2014 AHA/ACC/HRS Guidelines for Management of Patients With Atrial Fibrillation, patients with AF and a mechanical heart valve should not be prescribed the direct thrombin inhibitor dabigatran. When creating these measures, the writing committee determined that the science and 2014 AHA/ACC/HRS Guidelines for Management of Patients With Atrial Fibrillation justified expanding the measure to include Factor Xa inhibitors.	Additional data are required prior to making this measure a performance measure. The ability to elevate these measures to a performance measure will depend on the quality of data obtained once the measures are implemented. If it is found that patients are being provided with medications that can have a negative impact on patient safety, the writing committee may determine that the measure should be elevated to the status of a performance measure. However at this time we do not whether there is evidence to support elevation to a performance measure.
QM-14	Outpatient	Inappropriate Prescription of a Direct Thrombin or Factor Xa Inhibitor in Patients With Atrial Fibrillation With Mechanical Heart Valve		

The Comprehensive RWI Data Supplement table is available with this article at http://circoutcomes.ahajournals.org/lookup/suppl/doi:10.1161/HCQ.0000000000000018/-/DC1.

The American Heart Association requests that this document be cited as follows: Heidenreich PA, Solis P, Estes NAM 3rd, Fonarow GC, Jurgens CY, Marine JE, McManus DD, McNamara RL. 2016 ACC/AHA clinical performance and quality measures for adults with atrial fibrillation or atrial flutter: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures. *Circ Cardiovasc Qual Outcomes.* 2016;9:443–488. DOI: 10.1161/HCQ.0000000000000018.

This article has been copublished in the *Journal of the American College of Cardiology.*

***Circ Cardiovasc Qual Outcomes* is available at http://circoutcomes.ahajournals.org** **DOI: 10.1161/HCQ.0000000000000018**

Circ Cardiovasc Qual Outcomes. 2016;9:443-488

What is “non-valvular”? (Nov 2016)

Europace (2016) 18, 1609–1678
doi:10.1093/europace/euw295

ESC GUIDELINES

2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS

The Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC)

“Traditionally, patients with AF have been dichotomized into ‘valvular’ and ‘non-valvular’ AF. Although slightly different definitions have been used, **valvular AF mainly refers to AF patients that have either rheumatic valvular disease (predominantly mitral stenosis) or mechanical heart valves.** In fact, while AF implies an incremental risk for thrombo-embolism in patients with mitral valve stenosis, ***there is no clear evidence that other valvular diseases, including mitral regurgitation or aortic valve disease, need to be considered when choosing an anticoagulant or indeed to estimate stroke risk in AF.*** Therefore, **we have decided to replace the historic term ‘non-valvular’ AF with reference to the specific underlying conditions.**

Section 9: Stroke Prevention Therapy in Atrial Fibrillation Patients; 2016 ESC Guidelines for the management of atrial fibrillation (Europace (2016) 18, 1609–1678)

Europace (Nov 2016) 18, 1609–1678

Bottom Line: What is “non-valvular”?

- **Mechanical heart valves**
- **Moderate to severe mitral stenosis**

- **Everything else (bioprostheic valves, valve repair, valvuloplasty, aortic regurgitation, mitral regurgitation) is effectively “non-valvular”.**

Prevention of Thromboembolic Complications in Atrial Fibrillation (Ten things to consider)

- **You must know the** CHA_2DS_2-VASc score
- What does the term “non valvular atrial fibrillation mean”?
- *“Congestive heart failure” includes patients with normal EF*

Congestive heart failure includes patients with normal LV function (HF_pEF)

EBioMedicine 4 (2016) 26–39

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

Review

Emerging Tools for Stroke Prevention in Atrial Fibrillation

Christos Voukalis, Gregory Y.H. Lip, Eduard Shantsila *

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ARTICLE INFO

ABSTRACT

"Overall, although a clinical diagnosis of HF have not been universally predictive of stroke in AF, significant impairment of LV contractility or previous admission due to HF decompensation irrespective of LV systolic function clearly increases risk of stroke"

1. Introduction . . . 27
2. Risk Factors for Stroke in Atrial Fibrillation: A Brief Overview . . . 27
3. Risk Stratification Models for Stroke . . . 28
4. Risk of Bleeding . . . 28
5. Guidelines for Thromboprophylaxis in Atrial Fibrillation . . . 28
   5.1. Vitamin K Antagonists . . . 28
   5.2. Non-vitamin K Antagonist Oral Antagonists (NOACs) . . . 30
6. Cost Effectiveness of NOACs . . . 30
7. Net Clinical Benefit of Oral Anticoagulants . . . 31
8. Practical Considerations for Oral Anticoagulants . . . 31
9. Ethnicity and Thromboprophylaxis in Atrial Fibrillation . . . 31
10. Management of Anticoagulation Related Bleeding . . . 31
11. Specific Antidotes to NOACs . . . 32
12. Restarting Oral Anticoagulation After Ischaemic or Haemorrhagic Stroke and Major Gastrointestinal Bleeding . . . 32
13. Antiplatelet Therapy . . . 33
14. Oral Anticoagulation in Severe Renal Impairment (Creatinine Clearance < 15 ml/min) . . . 33
15. Oral Anticoagulation and Percutaneous Coronary Intervention . . . 34
16. Oral Anticoagulation and Cardioversion . . . 34
17. Catheter Ablation and Anticoagulation in Atrial Fibrillation . . . 35
18. Should Bridging Therapy Be Used or Not? . . . 35
19. Left Atrial Appendage Occlusion . . . 35
20. Thrombolysis in AF Patients Receiving Oral Anticoagulation . . . 35

Abbreviations: NVAF, non-valvular atrial fibrillation; TIA, transient ischaemic attack; TE, thromboembolic episode; LV, left ventricle; HF, heart failure; eGFR, estimated glomerular filtration rate; HTN, hypertension; DM, diabetes mellitus; RSM, risk stratification model; SE, systemic embolism; NICE, National Institute for Health and Care Excellence; PCI, percutaneous coronary intervention; INR, international normalised ratio; TTR, time in therapeutic range; NCB, net clinical benefit; CrCl, creatinine clearance; CKD, chronic kidney disease; ESRF, end stage renal failure; ICH, intracranial haemorrhage.

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http://dx.doi.org/10.1016/j.ebiom.2016.01.017

EBioMedicine 4 (2016) 26–39

Johnson & Johnson Pharmaceutical Research & Development*

Clinical Protocol

A Prospective, Randomized, Double-Blind, Double-Dummy, Parallel-Group, Multicenter, Event-Driven, Non-inferiority Study Comparing the Efficacy and Safety of Once-Daily Oral Rivaroxaban (BAY 59-7939) With Adjusted-Dose Oral Warfarin for the Prevention of Stroke and Non-Central Nervous System Systemic Embolism in Subjects With Non-Valvular Atrial Fibrillation

Protocol 39039039AFL3001; Phase 3
(EudraCT number 2006-004595-13)
BAY59-7939/11630
JNJ39039039 (rivaroxaban, BAY 59-7939)

Amendment INT-2

*Rivaroxaban (BAY-59-7939, JNJ-39039039) is being co-developed under a collaboration and license agreement between Bayer HealthCare AG (BHC) and Ortho McNeil Pharmaceuticals, Inc. (OMP) dated October 1, 2005. As determined by the parties, both BHC and OMP may use affiliated corporate entities to conduct this clinical trial. On behalf of OMP, such affiliates may include Johnson & Johnson Pharmaceutical Research & Development L.L.C. and Janssen-Cilag International N.V. The term "sponsor" or "designee" is used throughout the protocol to represent these various legal entities that have been identified to perform various clinical trial services; the actual sponsor or designee is identified on the Contact Information page that accompanies this protocol.

This study will be conducted under Food & Drug Administration IND regulations (CFR Part 312).

Issue/Report Date: 13 FEBRUARY 2009
Prepared by: Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Department: Drug Development
Document No.: EDMS-PSDB-5429061:5.0

2.1.8.3. Definition of Subgroup

The following subgroups determined by baseline characteristics will be examined with respect to the primary efficacy endpoint and the principal safety endpoint:

- Region (as specified earlier)
- Prior VKA use (yes, no)
- History of a prior stroke, TIA or non-CNS systemic embolism (yes, no)
- CHADS2 (<= 1, 2, 3, 4, 5, 6; moderate: 1-2, high: >=3)
- Prior chronic acetylsalicylic acid (ASA) use (yes, no)
- Sex (male, female)
- Age (<65, 65 to 75, >75; <75, >=75)
- Race (Caucasian, Black, Asian, other)
- Renal function (calculated CL_{CR} <50, 50 - 80, >80 mL/min)
- Body mass index (<=18.5, 18.5 - <=25, 25 - <=30, 30 - <=35, 35 - <=40, >40 kg/m2; <=25, 25 - <=35, >35 kg/m2)
- Weight (<=50, 50 - <=70, 70 - <=90, 90 - <= 110, >110 kg; <=70, 70 - <=90, >90 kg)
- Congestive heart failure (defined as (1) "LVEF<35% and/or clinical signs and symptoms" and/or (2) "preserve systolic function")
- Hypertension (yes, no)
- Diabetes (yes, no)
- AF Type (paroxysmal, persistent, permanent)
- Newly Diagnosed/ New Onset AF (yes, no)

Protocol for: Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365:883-91. DOI: 10.1056/NEJMoa1009638.

Bottom Line: CHF in CHA_2DS_2VASC

- **Includes any EF with HF diagnosis**
  - **HF_pEF and HF_rEF**

Prevention of Thromboembolic Complications in Atrial Fibrillation (Ten things to consider)

- **You must know the** CHA_2DS_2-VASc score
- What does the term “non valvular atrial fibrillation mean”?
- “Congestive heart failure” includes patients with normal EF
- *Hypertension includes “treated hypertension”*
  - *Common scenario: 66 yo normotensive male is referred to you for management of afib. His only medicine is Propranolol 10 mg bid.*

Hypertension includes “treated hypertension”

ORIGINAL CONTRIBUTION

Validation of Clinical Classification Schemes for Predicting Stroke

Results From the National Registry of Atrial Fibrillation

Brian F. Gage, MD, MSc

“We included a history of hypertension, rather than having blood pressure higher than 160 mm Hg, because even well controlled hypertension is a risk factor for stroke.”

peer review organizations representing 7 states were used to assemble a National Registry of AF (NRAF) consisting of 1733 Medicare beneficiaries aged 65 to 95 years who had nonrheumatic AF and were not prescribed warfarin at hospital discharge.

Main Outcome Measure Hospitalization for ischemic stroke, determined by Medicare claims data.

Results During 2121 patient-years of follow-up, 94 patients were readmitted to the hospital for ischemic stroke (stroke rate, 4.4 per 100 patient-years). As indicated by a c statistic greater than 0.5, the 2 existing classification schemes predicted stroke better than chance: c of 0.68 (95% confidence interval [CI], 0.65-0.71) for the scheme developed by the Atrial Fibrillation Investigators (AFI) and c of 0.74 (95% CI, 0.71-0.76) for the Stroke Prevention in Atrial Fibrillation (SPAF) III scheme. However, with a c statistic of 0.82 (95% CI, 0.80-0.84), the $CHADS_2$ index was the most accurate predictor of stroke. The stroke rate per 100 patient-years without antithrombotic therapy increased by a factor of 1.5 (95% CI, 1.3-1.7) for each 1-point increase in the $CHADS_2$ score: 1.9 (95% CI, 1.2-3.0) for a score of 0; 2.8 (95% CI, 2.0-3.8) for 1; 4.0 (95% CI, 3.1-5.1) for 2; 5.9 (95% CI, 4.6-7.3) for 3; 8.5 (95% CI, 6.3-11.1) for 4; 12.5 (95% CI, 8.2-17.5) for 5; and 18.2 (95% CI, 10.5-27.4) for 6.

Conclusion The 2 existing classification schemes and especially a new stroke risk index, $CHADS_2$, can quantify risk of stroke for patients who have AF and may aid in selection of antithrombotic therapy.

JAMA. 2001;285:2864-2870 www.jama.com

population is heterogeneous in terms of ischemic stroke risk. Subpopulations have annual stroke rates that range from less than 2% to more than 10%.[1-5] Because the relative risk reductions from warfarin sodium (62%) and aspirin (22%) therapy are consistent across these subpopulations,[2,6-8] the absolute benefit of antithrombotic therapy depends on the underlying risk of stroke. Although there has been agreement that warfarin therapy is favored when the risk of stroke is high and that aspirin is favored when the risk of stroke is low,[9,10] there has been little agreement about how to predict the risk of stroke.[11-13] Thus, an accurate, objective scheme to estimate the risk of stroke in the AF population would allow physicians and patients to choose antithrombotic therapy more judiciously.

The Atrial Fibrillation Investigators (AFI) pooled data from several trials to form a unified stroke classification scheme. Among trial participants who did not receive antithrombotic therapy, these researchers found that the risk of stroke increased by a factor of 1.4 per decade of age and by 3 clinical risk factors: hypertension, prior cerebral ischemia (either stroke or transient ischemic attack [TIA]), and diabetes mellitus (DM).[2,8] There were 3.9 to 10.4 strokes per 100 patient-years among participants randomized to no antithrombotic therapy who had at least 1 of the 3 clinical risk factors.[2,8] In contrast to

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JAMA 2001; 285:2864-2870

Hypertension includes “treated hypertension”

Trial Design

Apixaban for Reduction In Stroke and Other ThromboembolLic Events in Atrial Fibrillation (ARISTOTLE) trial: Design and rationale

Table I. Inclusion and exclusion criteria

Inclusion criteria

Age ≥18 y

Permanent or persistent AF or atrial flutter on ECG at enrollment; or AF or atrial flutter documented by ECG or as an episode ≥1 min on rhythm strip, Holter monitor, or intracardiac recording on 2 separate occasions at least 2 wk apart in 12 mo before enrollment

One or more of the following risk factors for stroke

- Age ≥75 y
- Prior stroke, TIA, or systemic embolus
- Symptomatic CHF within 3 mo or LV dysfunction with LVEF ≤40% by echocardiography, radionuclide study, or contrast angiography
- ~~Diabetes mellitus~~
- Hypertension requiring pharmacologic treatment

Women of childbearing potential must use contraception to avoid pregnancy during treatment period or for 2 wk after last dose of study medication, whichever is longer

All subjects must provide signed written informed consent

Am Heart J 2010;159:331-9

Bottom Line: HTN in CHA_2DS_2VASC

- For CHA_2DS_2VASc "treated hypertension" counts as 1 point in the scoring system

Prevention of Thromboembolic Complications in Atrial Fibrillation (Ten things to consider)

- **You must know the** CHA_2DS_2-VASc score
- What does the term “non valvular atrial fibrillation mean”?
- “Congestive heart failure” includes patients with normal EF
- Hypertension includes “treated hypertension”
- *What about aspirin for stroke prevention?*

What about aspirin for stroke prevention in Afib?

Annals of Internal Medicine | REVIEW

Meta-analysis: Antithrombotic Therapy to Prevent Stroke in Patients Who Have Nonvalvular Atrial Fibrillation

Robert G. Hart, MD; Lesly A. Pearce, MS; and Maria I. Aguilar, MD

Background: Atrial fibrillation is a strong independent risk factor for stroke.

Purpose: To characterize the efficacy and safety of antithrombotic agents for stroke prevention in patients who have atrial fibrillation, adding 13 recent randomized trials to a previous meta-analysis.

Data Sources: Randomized trials identified by using the Cochrane Stroke Group search strategy, 1966 to March 2007, unrestricted by language.

Study Selection: All published randomized trials with a mean follow-up of 3 months or longer that tested antithrombotic agents

64% (95% CI, 49% to 74%) and 22% (CI, 6% to 35%), respectively. Adjusted-dose warfarin was substantially more efficacious than antiplatelet therapy (relative risk reduction, 39% [CI, 22% to 52%]) (12 trials, 12 963 participants). Other randomized comparisons were inconclusive. Absolute increases in major extracranial hemorrhage were small (≤0.3% per year) on the basis of meta-analysis.

Limitation: Methodological features and quality varied substantially and often were incompletely reported.

Conclusions: Adjusted-dose warfarin and antiplatelet agents reduce stroke by approximately 60% and by approximately 20%,

"Adjusted-dose warfarin and antiplatelet agents reduce stroke by approximately 60% and by approximately 20%, respectively, in patients who have atrial fibrillation."

Nonvalvular atrial fibrillation is an important cause of disabling stroke whose incidence can be reduced by using antithrombotic prophylaxis. Our meta-analysis of the initial 16 randomized clinical trials that tested antithrombotic therapies for stroke prevention included approximately 10 000 participants (1). Since then, 13 randomized trials that included 18 140 additional patients with atrial fibrillation have been reported (**Table 1** [2–31]). Results of single, relatively small trials are sometimes difficult to interpret and often conflict, and meta-analysis is useful to assess the totality of trial evidence. We present an updated meta-analysis of all currently available randomized trials that extends observations about the efficacy and safety of antithrombotic therapies for preventing stroke in patients who have atrial fibrillation.

Methods

Search and Selection Process

We identified unconfounded randomized trials that tested long-term (≥12 weeks) use of antithrombotic agents in patients who had nonvalvular atrial fibrillation. We did a computerized search of the OVID and MEDLINE databases (from 1966 to March 2007, unrestricted by language) and of the Cochrane Stroke Group Trials Register and queried investigators working in the field (1). Trials that included patients who have prosthetic cardiac valves or mitral stenosis were not considered: double-blind and open-label trial designs were eligible. Two physician-reviewers independently extracted data from published sources and determined whether the trials met the inclusion criteria. Disagreements were resolved by joint review and consensus. We included 29 of 41 randomized trials that tested antithrombotic therapies in patients who had atrial fibrillation (**Table 1**), including 2 trials that reported results for subgroups of patients with atrial fibrillation from a larger number of patients without atrial fibrillation (13, 18). We identified 4 randomized trials that are ongoing (32–34) or have not been published (**Appendix Table 1**, available at www.annals.org) and excluded 8 randomized trials: 5 in which the treatment duration averaged 3 to 8 weeks (35–39), 1 in which the results for the subset of patients who had atrial fibrillation were not reported separately (40), 1 that included patients who had mitral stenosis (41), and 1 because of potential confounding in

See also:
Print
Editors' Notes 858
Web-Only
Appendix Tables
CME quiz
Conversion of figure and tables into slides

Ann Intern Med. 2007;146:857-867

What about aspirin for stroke prevention in Afib?

"Adjusted-dose v ly 60% and by approximately 2(

Table 1. **Randomized Trials of Antithrombotic Therapy for Patients with Nonvalvular Atrial Fibrillation***

Study, Year (Reference)	Participants, *n*	Interventions
AFASAK I, 1989 (2); 1990 (3)	1007	Warfarin†, aspirin, and placebo
BAATAF, 1990 (4)	420	Warfarin† and control
SPAF I, 1991 (5)	1330	Warfarin†, aspirin†, and placebo
CAFA, 1991 (6)	378	Warfarin and placebo
SPINAF, 1992 (7)	571	Warfarin† and placebo
EAFT, 1993 (8)‡	1007	Warfarin†, aspirin, and placebo
Harenberg et al., 1993 (9)	75	Low-molecular-weight heparin and control
SPAF II, 1994 (10)	1100	Warfarin and aspirin
SPAF III, 1996 (11)	1044	Warfarin† and low-dose warfarin plus aspirin
SIFA, 1997 (12)	916	Warfarin and indobufen
ESPS II, 1997 (13)	429	Aspirin, dipyridamole, aspirin plus dipyridamole, and placebo
AFASAK II, 1998 (14)	677	Warfarin, low-dose warfarin, aspirin, and low-dose warfarin plus aspirin
MWNAF, 1998 (15)	303	Warfarin and low-dose warfarin
PATAF, 1999 (16)‡	729	Warfarin, low-dose warfarin, and aspirin
LASAF, 1999 (17)	285	Aspirin daily, aspirin every other day, and control
UK-TIA, 1999 (18)	49	Aspirin (2 dosages) and placebo
JNAFESP, 2000 (19)	115	Warfarin (2 intensities)
FFAACS, 2001 (20)	157	Fluindione and fluindione plus aspirin
SPORTIF II, 2003 (21)	254	Ximelagatran (3 dosages) and warfarin
SPORTIF III, 2003 (22)	3407	Ximelagatran and warfarin
SAFT, 2003 (23)	668	Low-dose warfarin plus aspirin and control
NASPEAF, 2004 (25)	714§	Triflusal, acenocoumarol, or both
SPORTIF V, 2005 (24)	3922	Ximelagatran and warfarin
JAST, 2006 (26)	871	Aspirin and control
Vemmos et al., 2006 (27)	45	Warfarin, low-dose warfarin, and aspirin
ACTIVE-W, 2006 (28)	6706	Warfarin† and clopidogrel plus aspirin
PETRO, 2005 (29)	502	Dabigatran (3 dosages) with or without aspirin and warfarin
Chinese ATAFS, 2006 (30)	704	Warfarin and aspirin
WASPO, 2007 (31)	75	Warfarin and aspirin

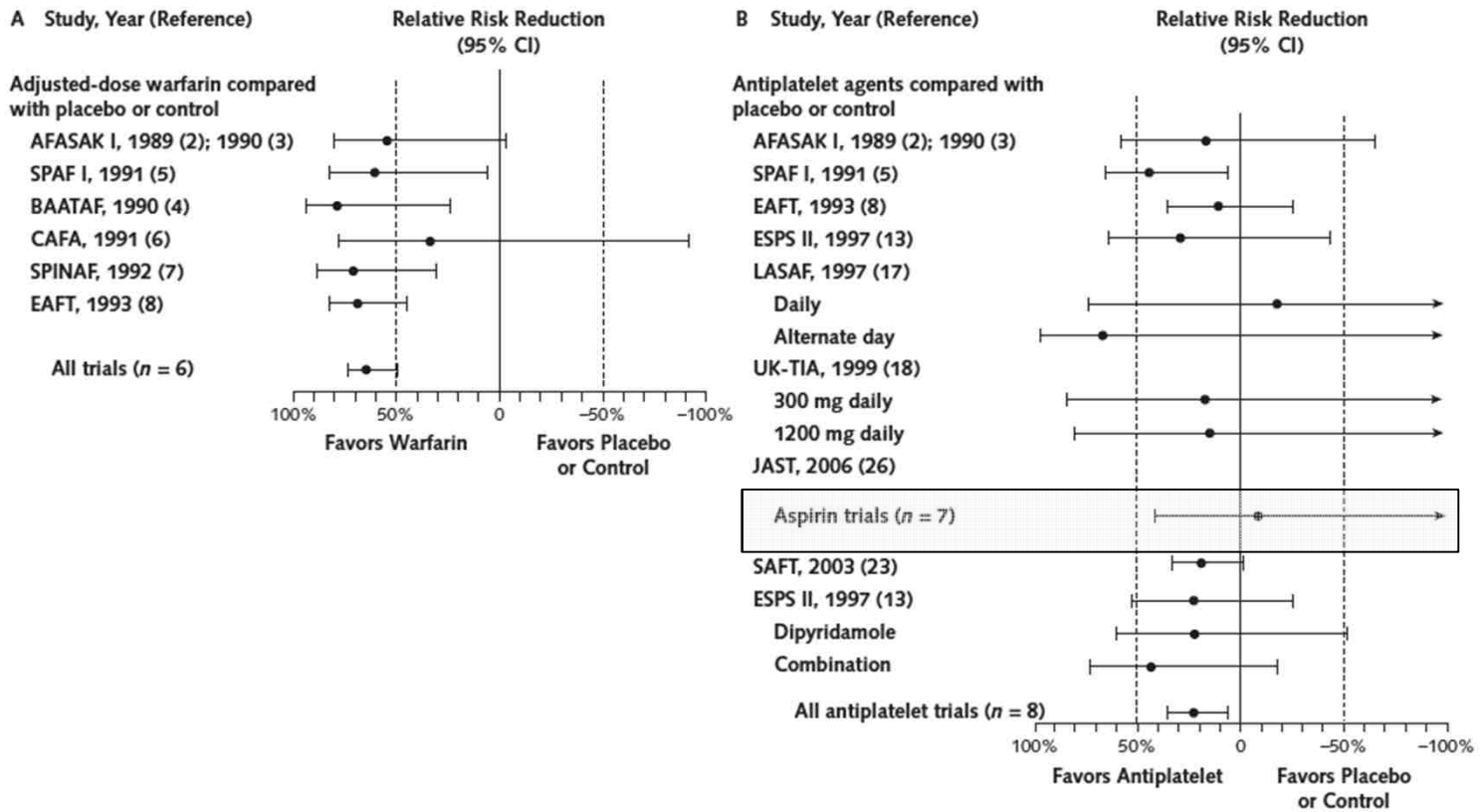
* Published trials in order of year of major publication. ACTIVE-W = Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events; AFASAK = Atrial Fibrillation, ASpirin, AntiKoagulation; ATAFS = Antithrombotic Therapy in Atrial Fibrillation Study; BAATAF = Boston Area Anticoagulation Trial for Atrial Fibrillation; CAFA = Canadian Atrial Fibrillation Anticoagulation; EAFT = European Atrial Fibrillation Trial; ESPS = European Stroke Prevention Study; FFAACS = Fluindione Fibrillation Auriculaire Aspirin et Contraste Spontané; JAST = Japan Atrial fibrillation Stroke Trial; JNAFESP = Japanese Nonvalvular Atrial Fibrillation Embolism Secondary Prevention; LASAF = Low-dose Aspirin, Stroke, Atrial Fibrillation; MWNAF = Minidose Warfarin in Nonrheumatic Atrial Fibrillation; NASPEAF = NAtional Study for Prevention of Embolism in Atrial Fibrillation; PATAF = Prevention of Arterial Thromboembolism in Atrial Fibrillation; PETRO = Prevention of Embolic and ThROmbotic events; SAFT = Swedish Atrial Fibrillation Trial; SIFA = Studio Italiano Fibrillazione Atriale; SPAF = Stroke Prevention in Atrial Fibrillation; SPINAF = Stroke Prevention in Nonrheumatic Atrial Fibrillation; SPORTIF = Stroke Prevention using an ORal Thrombin Inhibitor in atrial Fibrillation; UK-TIA = United Kingdom Transient Ischaemic Attack; WASPO = Warfarin vs. Aspirin for Stroke Prevention in Octogenarians.
† Indicates a statistically significant result reported for efficacy.
‡ Other oral vitamin K antagonists were used in addition to warfarin in a minority of participants.
§ High-risk patients are not included because most of them had mitral stenosis (that is, valvular atrial fibrillation) and the number of strokes for patients (n = 184) without mitral stenosis has not been reported separately.

Ann Intern Med. 2007;146:857-867

What about aspirin for stroke prevention in Afib?

"Adjusted … % and by approxima…

Figure. Relative effects of antithrombotic therapies on all stroke from randomized trials in patients with atrial fibrillation.



that included patients who have prosthetic cardiac valves or mitral stenosis were not considered: double-blind and

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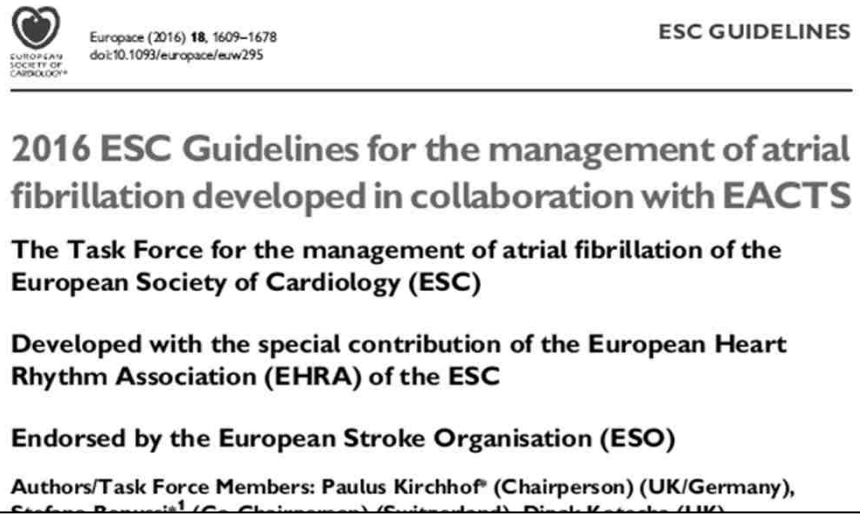


Europace (2016) 18, 1609–1678
doi:10.1093/europace/euw295

ESC GUIDELINES

2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS

The Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC)

Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC

Endorsed by the European Stroke Organisation (ESO)

Authors/Task Force Members: Paulus Kirchhof* (Chairperson) (UK/Germany),

"The bleeding risk on aspirin is not different to the bleeding risk on VKA or NOAC therapy, while VKA and NOACs, but not aspirin, effectively prevent strokes in AF patients."

Section 9: Stroke Prevention Therapy in Atrial Fibrillation Patients; 2016 ESC Guidelines for the management of atrial fibrillation (Europace (2016) 18, 1609–1678)

[2] Representing the European Stroke Association (ESO)

ESC Committee for Practice Guidelines (CPG) and National Cardiac Sodeties Reviewers can be found in the Appendix.

ESC entities having participated in the development of this document:

Associations: European Association for Cardiovascular Prevention and Rehabilitation (EACPR), European Association of Cardiovascular Imaging (EACVI), European Heart Rhythm Association (EHRA), Heart Failure Association (HFA).

Councils: Council on Cardiovascular Nursing and Allied Professions, Council for Cardiology Practice, Council on Cardiovascular Primary Care, Council on Hypertension.

Working Groups: Cardiac Cellular Electrophysiology, Cardiovascular Pharmacotherapy, Grown-up Congenital Heart Disease, Thrombosis, Valvular Heart Disease.

Disclaimer. The ESC Guidelines represent the views of the ESC and were produced after careful consideration of the scientific and medical knowledge and the evidence available at the time of their publication. The ESC is not responsible in the event of any contradiction, discrepancy and/or ambiguity between the ESC Guidelines and any other official recommendations or guidelines issued by the relevant public health authorities, in particular in relation to good use of healthcare or therapeutic strategies. Health professionals are encouraged to take the ESC Guidelines fully into account when exercising their clinical judgment, as well as in the determination and the implementation of preventive, diagnostic or therapeutic medical strategies; however, the ESC Guidelines do not override, in any way whatsoever, the individual responsibility of health professionals to make appropriate and accurate decisions in consideration of each patient's health condition and in consultation with that patient and, where appropriate and/or necessary, the patient's caregiver. Nor do the ESC Guidelines exempt health professionals from taking into full and careful consideration the relevant official updated recommendations or guidelines issued by the competent public health authorities, in order to manage each patient's case in light of the scientifically accepted data pursuant to their respective ethical and professional obligations. It is also the health professional's responsibility to verify the applicable rules and regulations relating to drugs and medical devices at the time of prescription.

Europace (Nov 2016) 18, 1609–1678

What about aspirin for stroke prevention in Afib?

Europace (2016) 18, 1609–1678
doi:10.1093/europace/euw295

ESC GUIDELINES

Recommendations for stroke prevention in patients with atrial fibrillation

Recommendations	Class[a]	Level[b]	Ref[c]
Oral anticoagulation therapy to prevent thromboembolism is recommended for all male AF patients with a CHA_2DS_2-VASc score of 2 or more.	I	A	38, 318–321, 354, 404
Oral anticoagulation therapy to prevent thromboembolism is recommended in all female AF patients with a CHA_2DS_2-VASc score of 3 or more.	I	A	38, 318–321, 354, 404
Oral anticoagulation therapy to prevent thromboembolism should be considered in male AF patients with a CHA_2DS_2-VASc score of 1, considering individual characteristics and patient preferences.	IIa	B	371, 375–377
Oral anticoagulation therapy to prevent thromboembolism should be considered in female AF patients with a CHA_2DS_2-VASc score of 2, considering individual characteristics and patient preferences.	IIa	B	371, 376, 377
Vitamin K antagonist therapy (INR 2.0–3.0 or higher) is recommended for stroke prevention in AF patients with			274
Antiplatelet monotherapy is not recommended for stroke prevention in AF patients, regardless of stroke risk.	III (harm)	A	38, 429, 430
When patients are treated with a vitamin K antagonist, time in therapeutic range (TTR) should be kept as high as possible and closely monitored.	I	A	395, 432, 441-444
AF patients already on treatment with a vitamin K antagonist may be considered for NOAC treatment if TTR is not well controlled despite good adherence, or if patient preference without contra-indications to NOAC (e.g. prosthetic valve).	IIb	A	39, 318, 319, 404, 408
Combinations of oral anticoagulants and platelet inhibitors increase bleeding risk and should be avoided in AF patients without another indication for platelet inhibition.	III (harm)	B	429, 445
In male or female AF patients without additional stroke risk factors, anticoagulant or antiplatelet therapy is not recommended for stroke prevention.	III (harm)	B	368, 371, 376, 377
NOACs (apixaban, dabigatran, edoxaban, and rivaroxaban) are not recommended in patients with mechanical heart valves (Level of evidence B) or moderate-to-severe mitral stenosis (Level of evidence C).	III (harm)	B C	318–321, 400, 404

AF = atrial fibrillation; CHA_2DS_2-VASc = Congestive Heart failure, hypertension, Age ≥75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65–74, and Sex (female); INR = international normalized ratio; NOAC = non-vitamin K antagonist oral anticoagulant; OAC = oral anticoagulation; TTR = time in therapeutic range; VKA = vitamin K antagonist.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

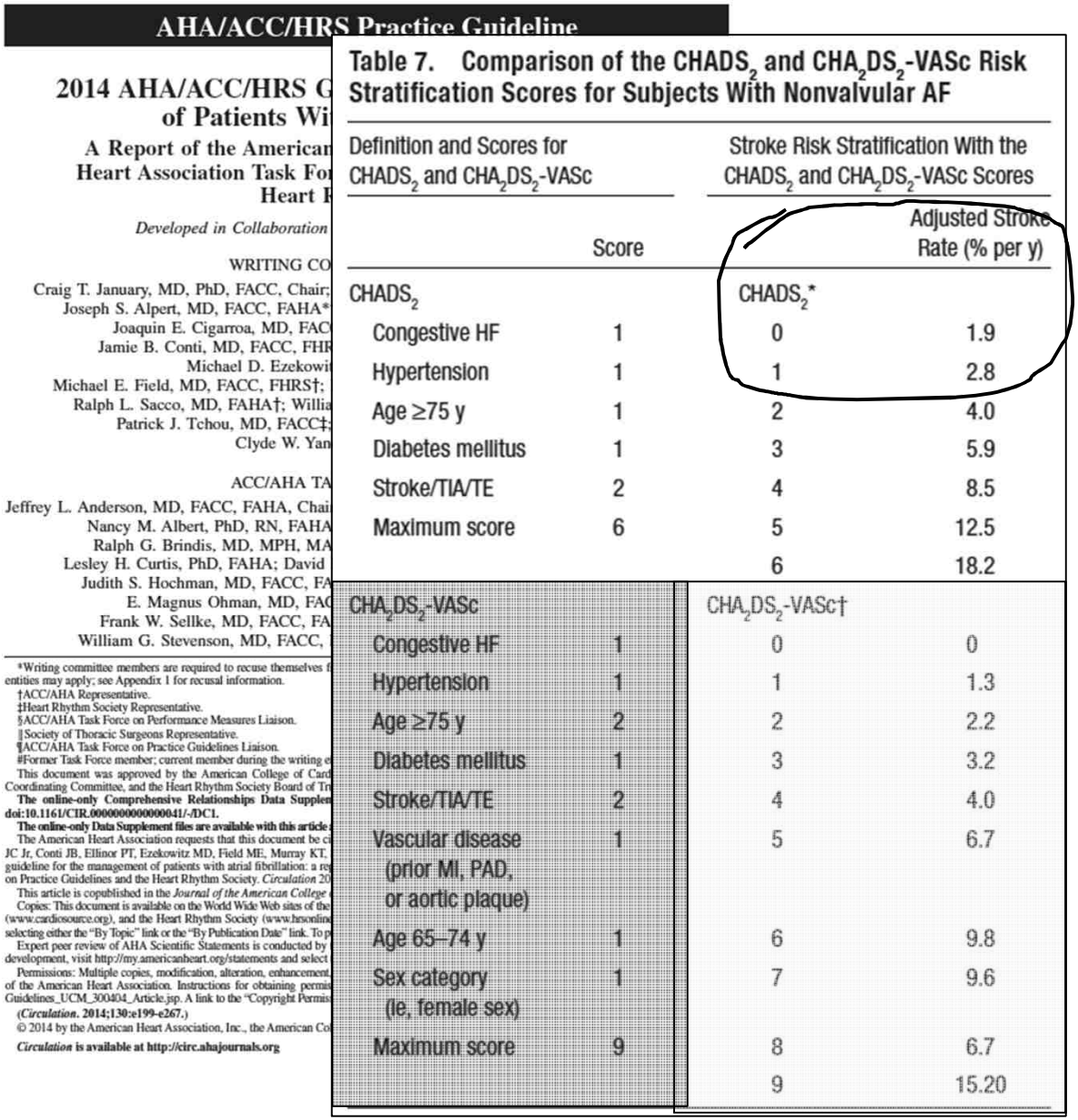
Europace (Nov 2016) 18, 1609–1678

Bottom line: Aspirin for stroke prevention in afib/aflutter

- Not an option as monotherapy for ANY patient with Afib to reduce the risk of stroke or TE

Prevention of Thromboembolic Complications in Atrial Fibrillation (Ten things to consider)

- **You must know the** CHA_2DS_2-VASc score
- What does the term “non valvular atrial fibrillation mean”?
- “Congestive heart failure” includes patients with normal EF
- Hypertension includes “treated hypertension”
- What about aspirin for stroke prevention?
- *At what point do I start anticoagulation?*



AHA/ACC/HRS Practice Guideline

2014 AHA/ACC/HRS G
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A Report of the American
Heart Association Task Fo
Heart F

Developed in Collaboration

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¶ACC/AHA Task Force on Practice Guidelines Liaison.
#Former Task Force member; current member during the writing e
This document was approved by the American College of Card
Coordinating Committee, and the Heart Rhythm Society Board of Tr
The online-only Comprehensive Relationships Data Supplen
doi:10.1161/CIR.0000000000000041/-/DC1.
The online-only Data Supplement files are available with this article
The American Heart Association requests that this document be ci
JC Jr, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT,
guideline for the management of patients with atrial fibrillation: a re
on Practice Guidelines and the Heart Rhythm Society. *Circulation* 20
This article is copublished in the *Journal of the American College*
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(*Circulation*. 2014;130:e199-e267.)
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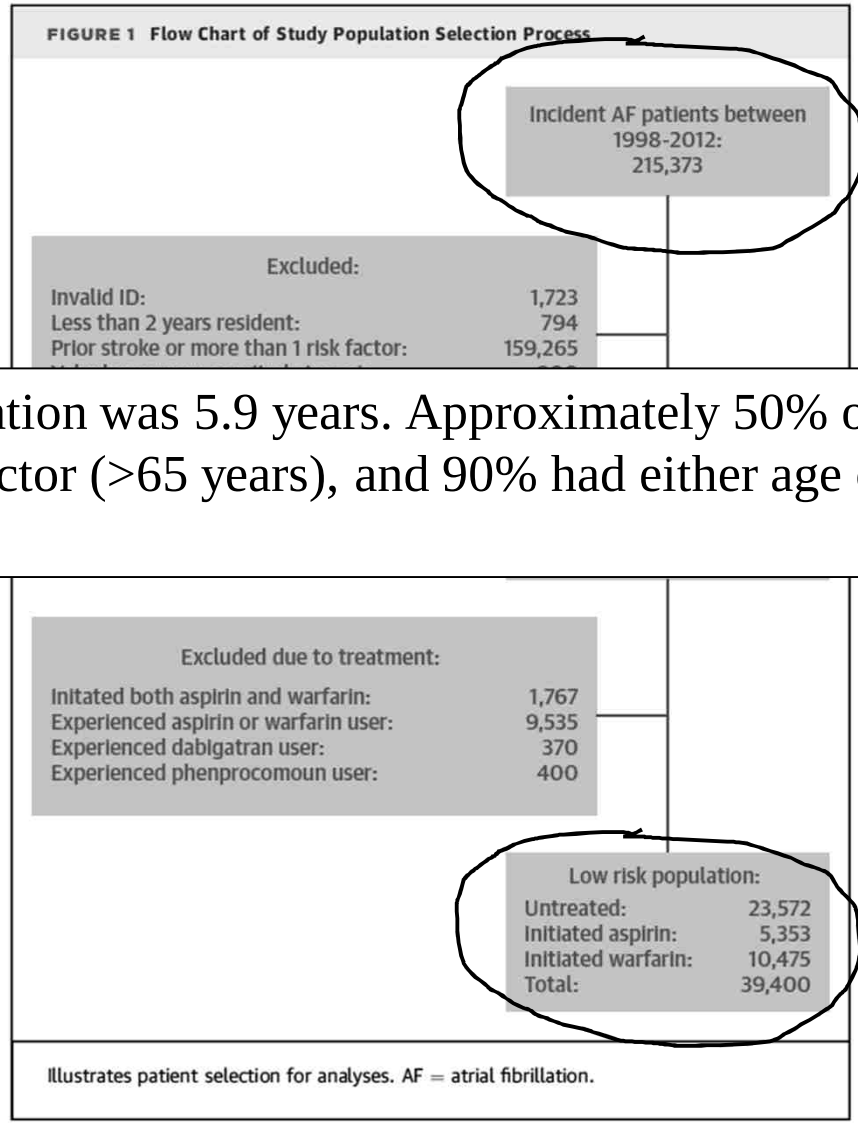
Table 7. Comparison of the $CHADS_2$ and CHA_2DS_2-VASc Risk Stratification Scores for Subjects With Nonvalvular AF

Definition and Scores for $CHADS_2$ and CHA_2DS_2-VASc		Stroke Risk Stratification With the $CHADS_2$ and CHA_2DS_2-VASc Scores	
	Score		Adjusted Stroke Rate (% per y)
$CHADS_2$		$CHADS_2$*	
Congestive HF	1	0	1.9
Hypertension	1	1	2.8
Age ≥75 y	1	2	4.0
Diabetes mellitus	1	3	5.9
Stroke/TIA/TE	2	4	8.5
Maximum score	6	5	12.5
		6	18.2
CHA_2DS_2-VASc		CHA_2DS_2-VASc†	
Congestive HF	1	0	0
Hypertension	1	1	1.3
Age ≥75 y	2	2	2.2
Diabetes mellitus	1	3	3.2
Stroke/TIA/TE	2	4	4.0
Vascular disease (prior MI, PAD, or aortic plaque)	1	5	6.7
Age 65–74 y	1	6	9.8
Sex category (ie, female sex)	1	7	9.6
Maximum score	9	8	6.7
		9	15.20

15-20% ten year risk of stroke

Circulation 2014;130:e199-e267

At what point do I start anticoagulation?

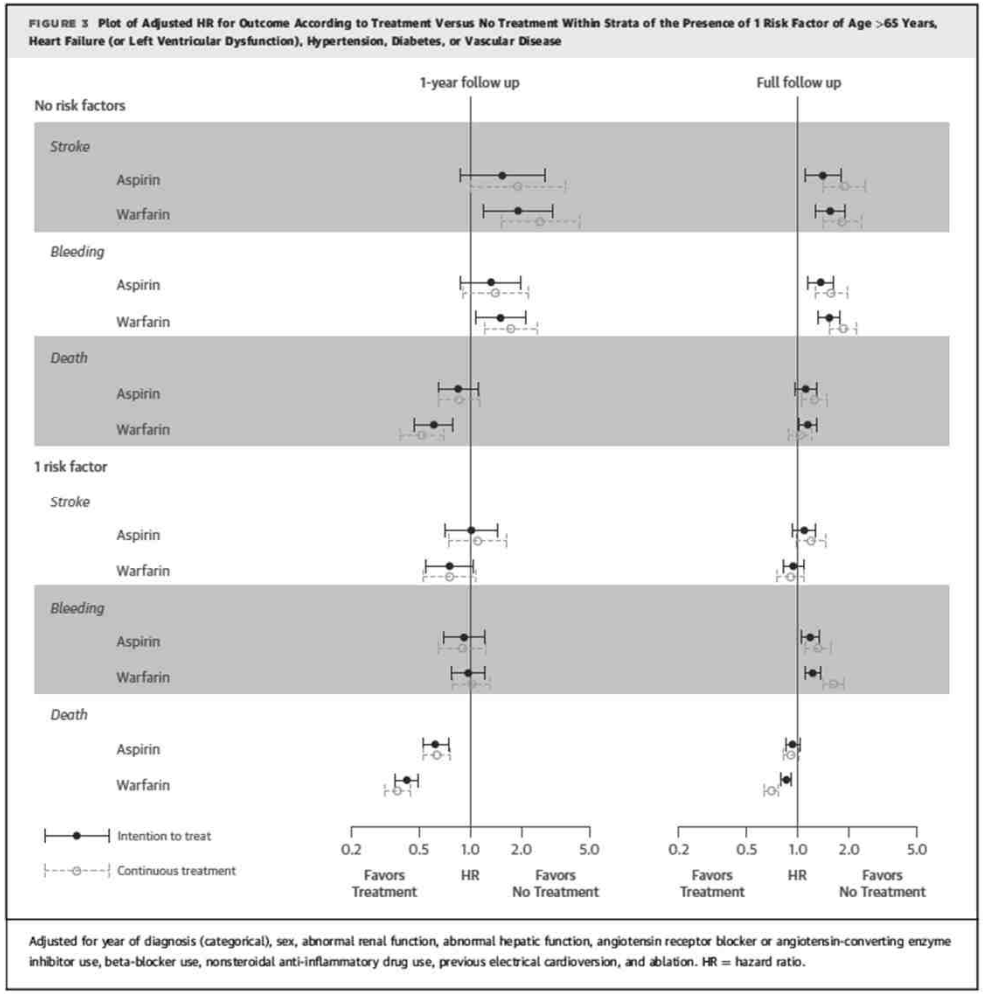


"The mean follow-up duration was 5.9 years. Approximately 50% of patients with 1 risk factor had age as the only risk factor (>65 years), and 90% had either age or hypertension as the risk factor."

J Am Coll Cardiol 2015;65:1385–94

At what point do I start anticoagulation?

FIGURE 3 Plot of Adjusted HR for Outcome According to Treatment Versus No Treatment Within Strata of the Presence of 1 Risk Factor of Age >65 Years, Heart Failure (or Left Ventricular Dysfunction), Hypertension, Diabetes, or Vascular Disease



Adjusted for year of diagnosis (categorical), sex, abnormal renal function, abnormal hepatic function, angiotensin receptor blocker or angiotensin-converting enzyme inhibitor use, beta-blocker use, nonsteroidal anti-inflammatory drug use, previous electrical cardioversion, and ablation. HR = hazard ratio.

ported this study. The sponsor had no role in the study design; in the collection, analysis, and interpretation of the data; in the writing of this report; or in the decision to submit the paper for publication. Dr. Lip has served as a consultant for Bayer, Astellas, Merck & Co., AstraZeneca, Sanofi, Bristol-Myers Squibb/Pfizer, Daiichi-Sankyo, Medtronic, Biotronik, Portola, and Boehringer Ingelheim; and has been on the Speakers Bureau for Bayer, Bristol-Myers Squibb/Pfizer, Boehringer Ingelheim, Medtronic, Daiichi-Sankyo, and Sanofi. Dr. Larsen has served as an investigator for Janssen Scientific Affairs, LLC, and Boehringer Ingelheim; and

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At what point do I start anticoagulation?

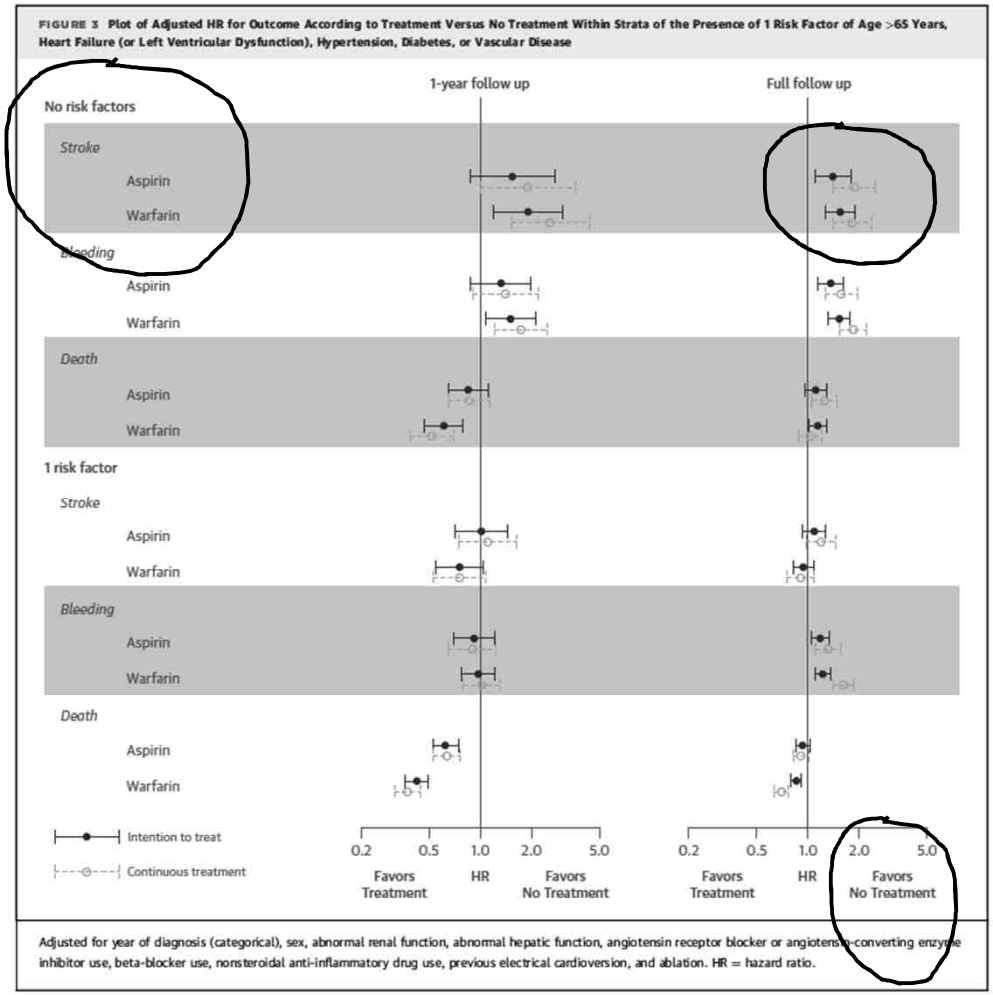

FIGURE 3 Plot of Adjusted HR for Outcome According to Treatment Versus No Treatment Within Strata of the Presence of 1 Risk Factor of Age >65 Years, Heart Failure (or Left Ventricular Dysfunction), Hypertension, Diabetes, or Vascular Disease

Adjusted for year of diagnosis (categorical), sex, abnormal renal function, abnormal hepatic function, angiotensin receptor blocker or angiotensin-converting enzyme inhibitor use, beta-blocker use, nonsteroidal anti-inflammatory drug use, previous electrical cardioversion, and ablation. HR = hazard ratio.

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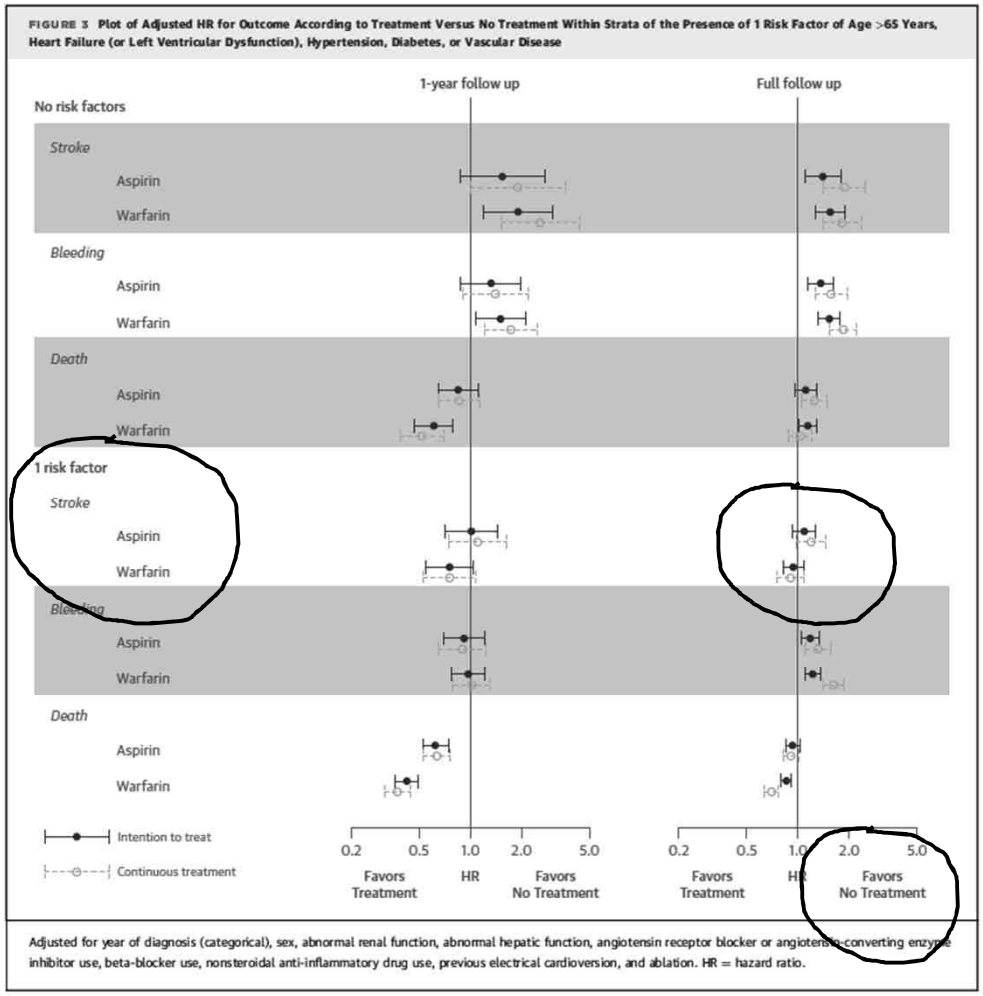
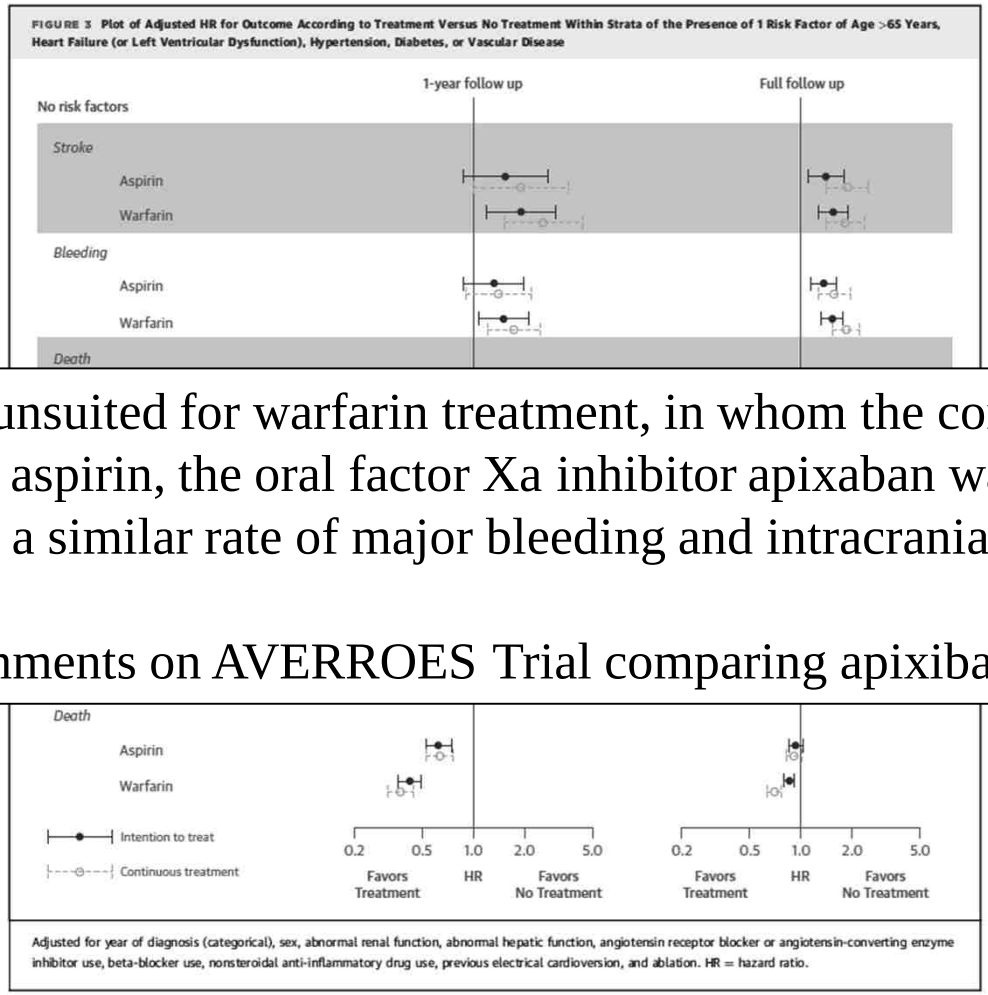
At what point do I start anticoagulation?



ported this study. The sponsor had no role in the study design; in the collection, analysis, and interpretation of the data; in the writing of this report; or in the decision to submit the paper for publication. Dr. Lip has served as a consultant for Bayer, Astellas, Merck & Co., AstraZeneca, Sanofi, Bristol-Myers Squibb/Pfizer, Daiichi-Sankyo, Medtronic, Biotronik, Portola, and Boehringer Ingelheim; and has been on the Speakers Bureau for Bayer, Bristol-Myers Squibb/Pfizer, Boehringer Ingelheim, Medtronic, Daiichi-Sankyo, and Sanofi. Dr. Larsen has served as an investigator for Janssen Scientific Affairs, LLC, and Boehringer Ingelheim; and

J Am Coll Cardiol 2015;65:1385–94

At what point do I start anticoagulation?



"Even among patients unsuited for warfarin treatment, in whom the common practice previously was to offer aspirin, the oral factor Xa inhibitor apixaban was superior to aspirin for stroke prevention, with a similar rate of major bleeding and intracranial hemorrhage."

Lip, GYH, et al. re comments on AVERROES Trial comparing apixiban vs. ASA

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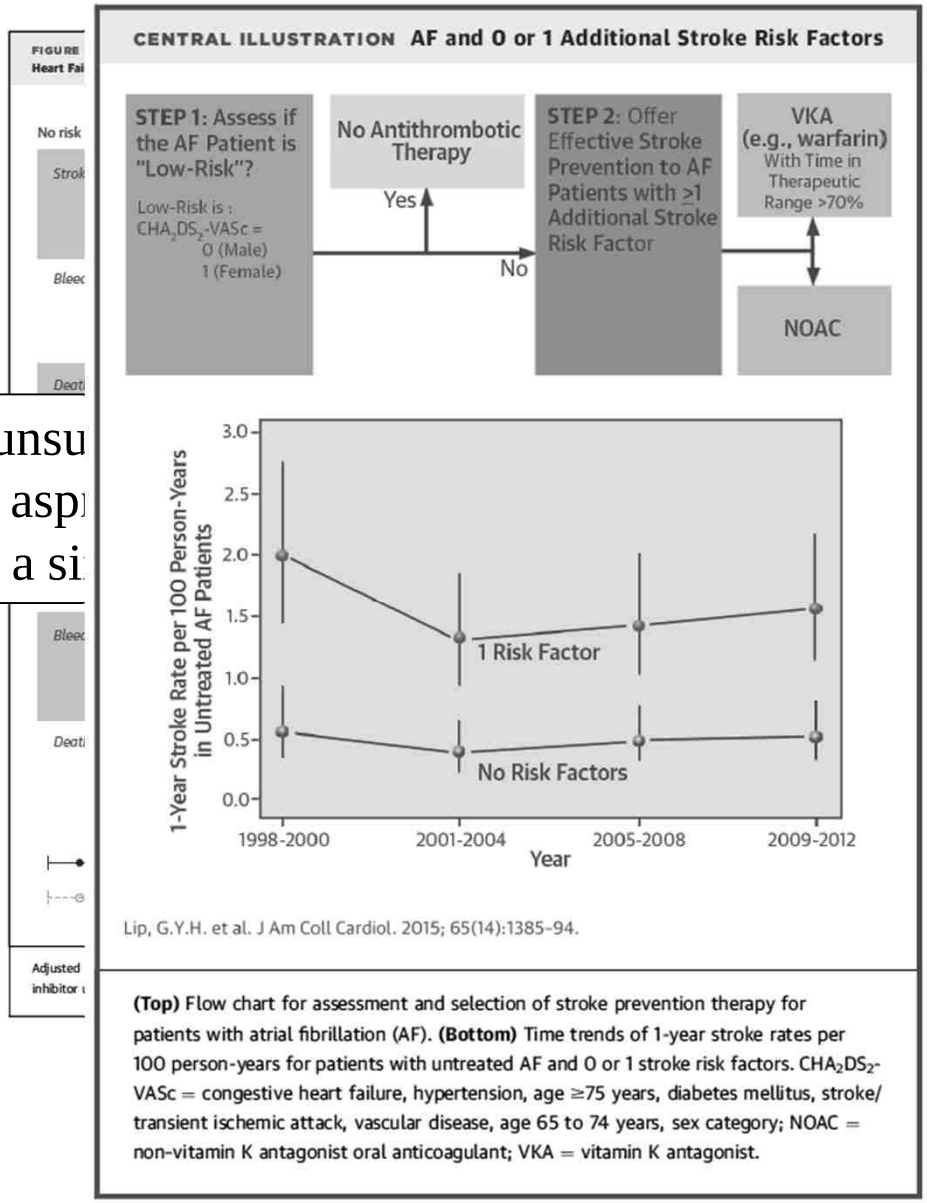

(Top) Flow chart for assessment and selection of stroke prevention therapy for patients with atrial fibrillation (AF). **(Bottom)** Time trends of 1-year stroke rates per 100 person-years for patients with untreated AF and 0 or 1 stroke risk factors. CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65 to 74 years, sex category; NOAC = non-vitamin K antagonist oral anticoagulant; VKA = vitamin K antagonist.

J Am Coll Cardiol 2015;65:1385–94

At what point do I start anticoagulation?

Europace (2016) 18, 1609–1678
doi:10.1093/europace/euw295

ESC GUIDELINES

Recommendations for stroke prevention in patients with atrial fibrillation

Recommendations	Class[a]	Level[b]	Ref[c]
Oral anticoagulation therapy to prevent thromboembolism is recommended for all male AF patients with a CHA_2DS_2-VASc score of 2 or more.	I	A	38, 318–321, 354, 404
Oral anticoagulation therapy to prevent thromboembolism is recommended in all female AF patients with a CHA_2DS_2-VASc score of 3 or more.	I	A	38, 318–321, 354, 404
Oral anticoagulation therapy to prevent thromboembolism should be considered in male AF patients with a CHA_2DS_2-VASc score of 1, considering individual characteristics and patient preferences.	IIa	B	371, 375–377
Oral anticoagulation therapy to prevent thromboembolism should be considered in female AF patients with a CHA_2DS_2-VASc score of 2, considering individual characteristics and patient preferences.	IIa	B	371, 376, 377
Vitamin K antagonist therapy (INR 2.0–3.0 or higher) is recommended for stroke prevention in AF patients with moderate-to-severe mitral stenosis or mechanical heart valves.	I	B	274, 435–440
When oral anticoagulation is initiated in a patient with AF who is eligible for a NOAC (apixaban, dabigatran, edoxaban, or rivaroxaban), a NOAC is recommended in preference to a vitamin K antagonist.	I	A	39, 318–321, 404
When patients are treated with a vitamin K antagonist, time in therapeutic range (TTR) should be kept as high as possible and closely monitored.	I	A	395, 432, 441-444
AF patients already on treatment with a vitamin K antagonist may be considered for NOAC treatment if TTR is not well controlled despite good adherence, or if patient preference without contra-indications to NOAC (e.g. prosthetic valve).	IIb	A	39, 318, 319, 404, 408
Combinations of oral anticoagulants and platelet inhibitors increase bleeding risk and should be avoided in AF patients without another indication for platelet inhibition.	III (harm)	B	429, 445
In male or female AF patients without additional stroke risk factors, anticoagulant or antiplatelet therapy is not recommended for stroke prevention.	III (harm)	B	368, 371, 376, 377
Antiplatelet monotherapy is not recommended for stroke prevention in AF patients, regardless of stroke risk.	III (harm)	A	38, 429, 430
NOACs (apixaban, dabigatran, edoxaban, and rivaroxaban) are not recommended in patients with mechanical heart valves (Level of evidence B) or moderate-to-severe mitral stenosis (Level of evidence C).	III (harm)	B C	318–321, 400, 404

Europace (Nov 2016) 18, 1609–1678

Prevention of Thromboembolic Complications in Atrial Fibrillation (Ten things to consider)

- **You must know the** CHA_2DS_2-VASc score
- What does the term “non valvular atrial fibrillation mean”?
- “Congestive heart failure” includes patients with normal EF
- Hypertension includes “treated hypertension”
- At what point do I start anticoagulation?
- What about aspirin for stroke prevention?
- *Coumadin or NOAC? – “Time in Therapeutic Range” and dosing*

Coumadin or NOAC?

Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials

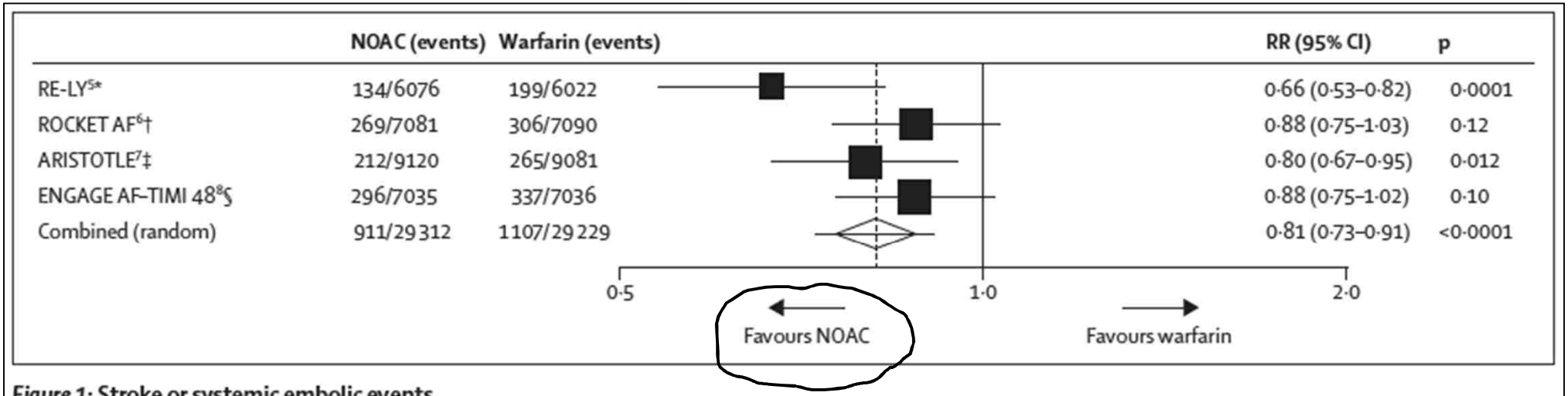

***Figure 1*: Stroke or systemic embolic events**

Data are n/N, unless otherwise indicated. Heterogeneity: I^2=47%; p=0·13. NOAC=new oral anticoagulant. RR=risk ratio. *Dabigatran 150 mg twice daily. †Rivaroxaban 20 mg once daily. ‡Apixaban 5 mg twice daily. §Edoxaban 60 mg once daily.

Introduction

Atrial fibrillation, the most common sustained cardiac arrhythmia, predisposes patients to an increased risk of embolic stroke and has a higher mortality than sinus rhythm.[1,2] Until 2009, warfarin and other vitamin K antagonists were the only class of oral anticoagulants available. Although these drugs are highly effective in prevention of thromboembolism, their use is limited by a narrow therapeutic index that necessitates frequent monitoring and dose adjustments resulting in substantial risk and inconvenience. This limitation has translated into poor patient adherence and probably contributes to the systematic underuse of vitamin K antagonists for stroke prevention.[3,4]

Several new oral anticoagulants have been developed that dose-dependently inhibit thrombin or activated factor X (factor Xa) and offer potential advantages over vitamin K antagonists, such as rapid onset and offset of action, absence of an effect of dietary vitamin K intake on their activity, and fewer drug interactions. The

www.thelancet.com Published online December 4, 2013 http://dx.doi.org/10.1016/S0140-6736(13)62343-0

Lancet. 2014 Mar 15;383(9921):955-62

Coumadin or NOAC?

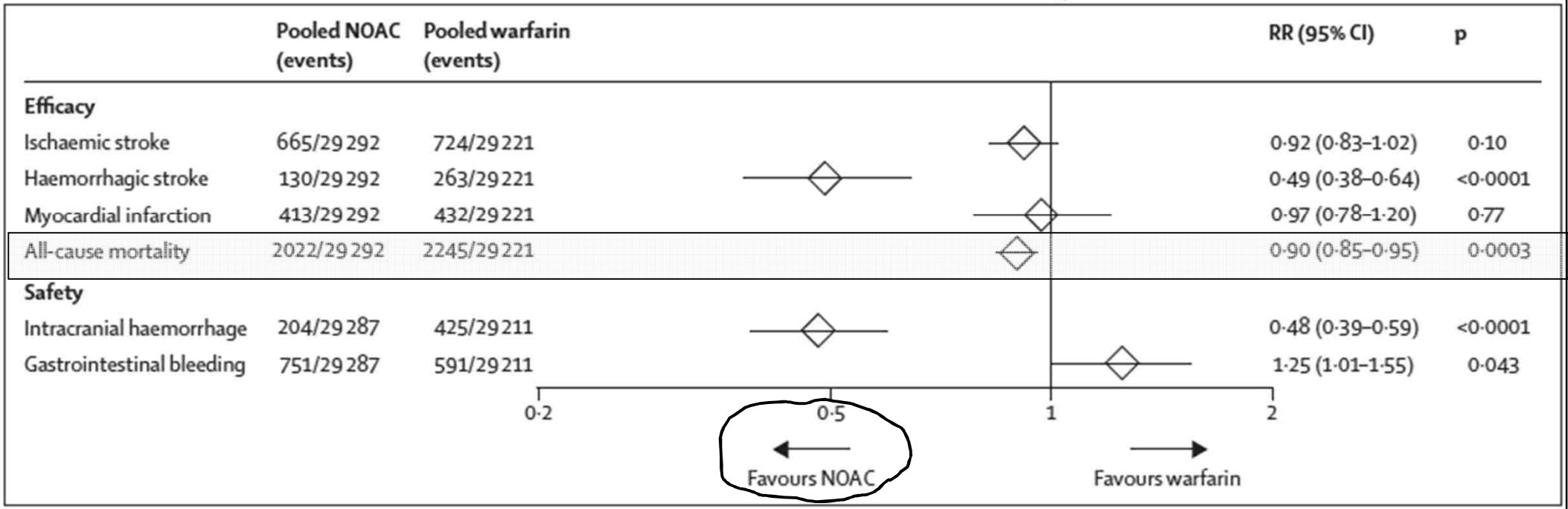

***Figure 2*: Secondary efficacy and safety outcomes**

Data are n/N, unless otherwise indicated. Heterogeneity: ischaemic stroke I^2=32%, p=0·22; haemorrhagic stroke I^2=34%, p=0·21; myocardial infarction I^2=48%, p=0·13; all-cause mortality I^2=0%, p=0·81; intracranial haemorrhage I^2=32%, p=0·22; gastrointestinal bleeding I^2=74%, p=0·009. NOAC=new oral anticoagulant. RR=risk ratio.

Introduction

Atrial fibrillation, the most common sustained cardiac arrhythmia, predisposes patients to an increased risk of embolic stroke and has a higher mortality than sinus rhythm.[1,2] Until 2009, warfarin and other vitamin K antagonists were the only class of oral anticoagulants available. Although these drugs are highly effective in prevention of thromboembolism, their use is limited by a narrow therapeutic index that necessitates frequent monitoring and dose adjustments resulting in substantial risk and inconvenience. This limitation has translated into poor patient adherence and probably contributes to the systematic underuse of vitamin K antagonists for stroke prevention.[3,4]

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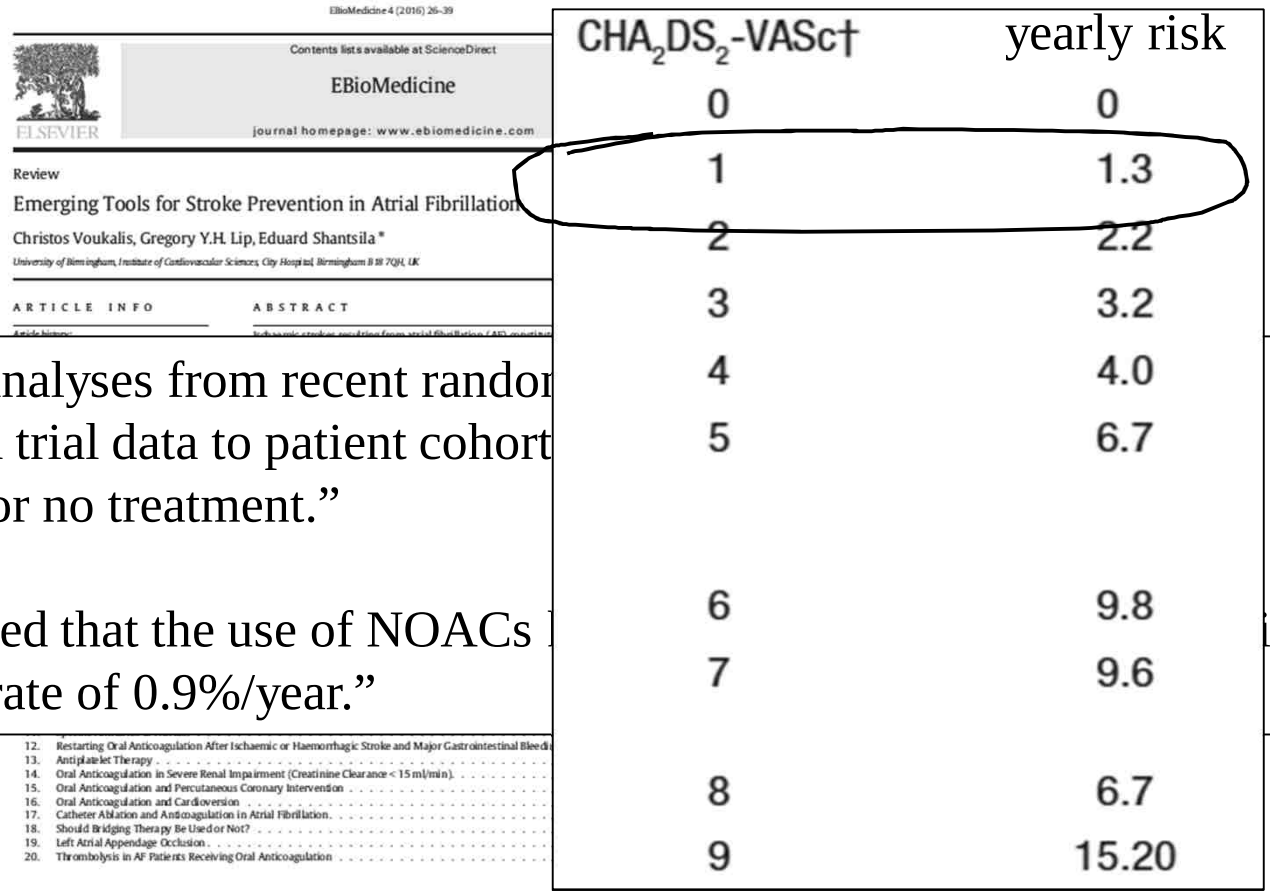
Coumadin or NOAC?



EBioMedicine 4 (2016) 26–39

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Review

Emerging Tools for Stroke Prevention in Atrial Fibrillation

Christos Voukalis, Gregory Y.H. Lip, Eduard Shantsila *

University of Birmingham, Institute of Cardiovascular Sciences, City Hospital, Birmingham B 18 7QH, UK

ARTICLE INFO

ABSTRACT

CHA_2DS_2-VASc†	yearly risk
0	0
1	1.3
2	2.2
3	3.2
4	4.0
5	6.7
6	9.8
7	9.6
8	6.7
9	15.20

"Net clinical benefit (NCB) analyses from recent rando
analyses applying the clinical trial data to patient cohort
NOACs vs warfarin, aspirin or no treatment."

"Indeed, one analysis estimated that the use of NOACs
OAC at an ischaemic stroke rate of 0.9%/year."

12. Restarting Oral Anticoagulation After Ischaemic or Haemorrhagic Stroke and Major Gastrointestinal Bleedi
13. Antiplatelet Therapy
14. Oral Anticoagulation in Severe Renal Impairment (Creatinine Clearance < 15 ml/min).
15. Oral Anticoagulation and Percutaneous Coronary Intervention
16. Oral Anticoagulation and Cardioversion
17. Catheter Ablation and Anticoagulation in Atrial Fibrillation.
18. Should Bridging Therapy Be Used or Not?
19. Left Atrial Appendage Occlusion
20. Thrombolysis in AF Patients Receiving Oral Anticoagulation

Abbreviations: NVAF, non-valvular atrial fibrillation; TIA, transient ischaemic attack; TE, thromboembolic episode; LV, left ventricle; HF, heart failure; eGFR, estimated glomerular filtration rate; HTN, hypertension; DM, diabetes mellitus; RSM, risk stratification model; SE, systemic embolism; NICE, National Institute for Health and Care Excellence; PCI, percutaneous coronary intervention; INR, international normalised ratio; TTR, time in therapeutic range; NCB, net clinical benefit; CrCl, creatinine clearance; CKD, chronic kidney disease; ESRF, end stage renal failure; ICH, intracranial haemorrhage.

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http://dx.doi.org/10.1016/j.ebiom.2016.01.017

EBioMedicine 4 (2016) 26–39

Coumadin or NOAC—the problem of TTR

REVIEW ARTICLE

Current Trial-Associated Outcomes With Warfarin in Prevention of Stroke in Patients With Nonvalvular Atrial Fibrillation

A Meta-analysis

Shikhar Agarwal, MD, MPH, CPH; Rory Hachamovitch, MD, MS; Venu Menon, MD

Background: Although several new antithrombotic agents have been developed for stroke prevention in patients with nonvalvular atrial fibrillation (AF), many patients will continue to be treated with warfarin worldwide. We performed a meta-analysis of safety and efficacy outcomes in patients with AF treated with warfarin for stroke prevention in large contemporary randomized controlled trials (RCTs).

Methods: We searched the MEDLINE, EMBASE, and Cochrane databases for relevant studies; RCTs comparing warfarin with an alternative thromboprophylaxis strategy with at least 400 patients in the warfarin arm and reporting stroke as an efficacy outcome were included.

Results: Eight RCTs with 55 789 patient-years of warfarin therapy follow-up were included. Overall time spent in the therapeutic range was 55% to 68%. The annual incidence of stroke or systemic embolism in patients with AF taking warfarin was estimated to be 1.66% (95% CI, 1.41%-1.91%). Major bleeding rates varied from 1.40% to 3.40% per year across the studies. The risk of stroke per year was significantly higher in elderly patients (2.27%), female patients (2.12%), patients with a history of stroke (2.64%), and patients reporting no previous exposure to vitamin K antagonists (1.96%). There was a significant increase in the annual incidence of stroke with progressively increasing $CHADS_2$ (congestive heart failure, hypertension, age, diabetes, and prior stroke) scores.

Conclusions: Current use of warfarin as a stroke prevention agent in patients with AF is associated with a low rate of residual stroke or systemic embolism estimated to be 1.66% per year. Compared with a previous meta-analysis, there has been significant improvement in the proportion of time spent in therapeutic anticoagulation, with a resultant decline in observed stroke rates.

Arch Intern Med. 2012;172(8):623-631.
Published online March 26, 2012.
doi:10.1001/archinternmed.2012.121

Nonvalvular atrial fibrillation (AF) is associated with a 5-fold increase in the risk of ischemic stroke and has been implicated as a causal factor in as many as 15% to 20% of all ischemic strokes.[1] A meta-analysis[2] of 6 randomized controlled trials (RCTs) comparing the efficacy of warfarin with that of placebo in stroke prevention in AF demonstrated a significant reduction in stroke and all-cause mortality in patients treated with warfarin compared with no antithrombotic treatment. Patients with AF at the highest risk of stroke, particularly those with previous stroke or transient ischemic attack (TIA), derived the greatest absolute risk reduction with warfarin compared with aspirin or no antithrombotic treatment.[2] Although a more recent meta-analysis[3] evaluating the efficacy of available antithrombotic therapies for patients with AF included 29 RCTs, no new trials comparing warfarin with placebo were available for inclusion.

See Invited Commentary at end of article

CME available online at www.jamaarchivescme.com and questions on page 607

Novel antithrombotic agents have been developed as alternatives to warfarin (eg, direct thrombin inhibitors[4-6] and selective factor Xa inhibitors[7-9]), several of which have been demonstrated to be superior to warfarin in clinical trials.[6,8,9] In addition to therapeutic efficacy, these newer agents are easy to administer, are consistent in effect, and lack interaction with other medications and

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Arch Intern Med. 2012;172(8):623-631

Time in Therapeutic Range (TTR) for Selected Major Trials (Warfarin)

Table 1. Characteristics of the 8 Included Trials[a]

Source[b]	Inclusion Criteria	Primary End Point	Definition of Major Bleeding
ACTIVE W,[14] 2006	AF with age ≥75 y or treatment for hypertension or previous stroke/TIA/non-CNS embolism or LVEF <45% or PAD AF with age 55-74 y with DM or previous CAD	Composite of stroke, non-CNS embolism, MI, or vascular death	Bleeding associated with death, drop in hemoglobin ≥5.0 g/dL, hypotension requiring inotropes, ≥2-U RBC transfusion, intraocular bleeding, intracranial bleeding, or need for surgical intervention other than vascular repair
SPORTIF V,[4] 2005	AF with age ≥75 y or hypertension or LV dysfunction (LVEF <40% or symptomatic systolic or diastolic heart failure) or previous stroke/TIA/non-CNS embolism AF with age >65 y with CAD or DM	Composite of stroke or non-CNS embolism	Bleeding associated with death, drop in hemoglobin ≥2.0 g/dL, ≥2-U RBC transfusion, or bleeding that was intracranial (excluding intracerebral), retroperitoneal, spinal, ocular, pericardial, or atraumatic articular
BAFTA,[13] 2007	AF or atrial flutter with age ≥75 y with no contraindications to warfarin use	Composite of stroke, intracranial hemorrhage, or non-CNS embolism	Extracranial bleeding that was fatal or required transfusion or surgery or intracranial hemorrhage including hemorrhagic stroke
Amadeus,[7] 2008	AF with age ≥75 y or treatment for hypertension, LV dysfunction, previous ischemic stroke/TIA/ non-CNS embolism AF with age >65 y with DM or CAD	Composite of stroke or non-CNS embolism	Bleeding associated with death, drop in hemoglobin ≥2.0 g/dL, ≥2-U RBC transfusion, intracranial bleeding, or bleeding affecting a "critical anatomical site"
SPORTIF III,[5] 2003	AF with age ≥75 y or hypertension (BP <180/100 mm Hg) needing treatment or LV dysfunction (LVEF <40% or symptomatic CHF) or previous stroke/TIA/non-CNS embolism AF with age >65 y with DM or CAD	Composite of stroke or non-CNS embolism	Bleeding associated with death, drop in hemoglobin ≥2.0 g/dL, ≥2-U RBC transfusion, or bleeding affecting a critical anatomical site (intracranial, spinal, intraocular, retroperitoneal, pericardial, or atraumatic intra-articular)
RE-LY,[6] 2009	AF with age ≥75 y or LVEF <40% or NYHA class II or higher symptoms or previous stroke/TIA/non-CNS embolism AF with age >65 y with DM or hypertension or CAD	Composite of stroke or non-CNS embolism	Bleeding causing a reduction in hemoglobin ≥2.0 g/dL, ≥2-U RBC transfusion, or "symptomatic bleeding in a critical area or organ"
ROCKET-AF,[8] 2011	AF with previous stroke/TIA/ non-CNS embolism AF with a $CHADS_2$ score ≥2	Composite of stroke or non-CNS embolism	Bleeding associated with death, drop in hemoglobin ≥2.0 g/dL, ≥2-U RBC transfusion, permanent disability, or bleeding affecting a critical anatomical site (intracranial, spinal, ocular, pericardial, articular, retroperitoneal, or intramuscular with compartment syndrome)
ARISTOTLE,[9] 2011	AF or atrial flutter with age ≥75 y or hypertension requiring treatment, DM, symptomatic heart failure, LVEF <40%, previous stroke/TIA/ non-CNS embolism	Composite of stroke or non-CNS embolism	Bleeding associated with death, drop in hemoglobin ≥2.0 g/dL, ≥2-U RBC transfusion, or bleeding affecting a critical anatomical site (intracranial, spinal, intraocular, retroperitoneal, pericardial, intra-articular, or intramuscular with compartment syndrome)

Arch Intern Med. 2012;172(8):623-631

Time in Therapeutic Range (TTR) for Selected Major Trials (Warfarin)

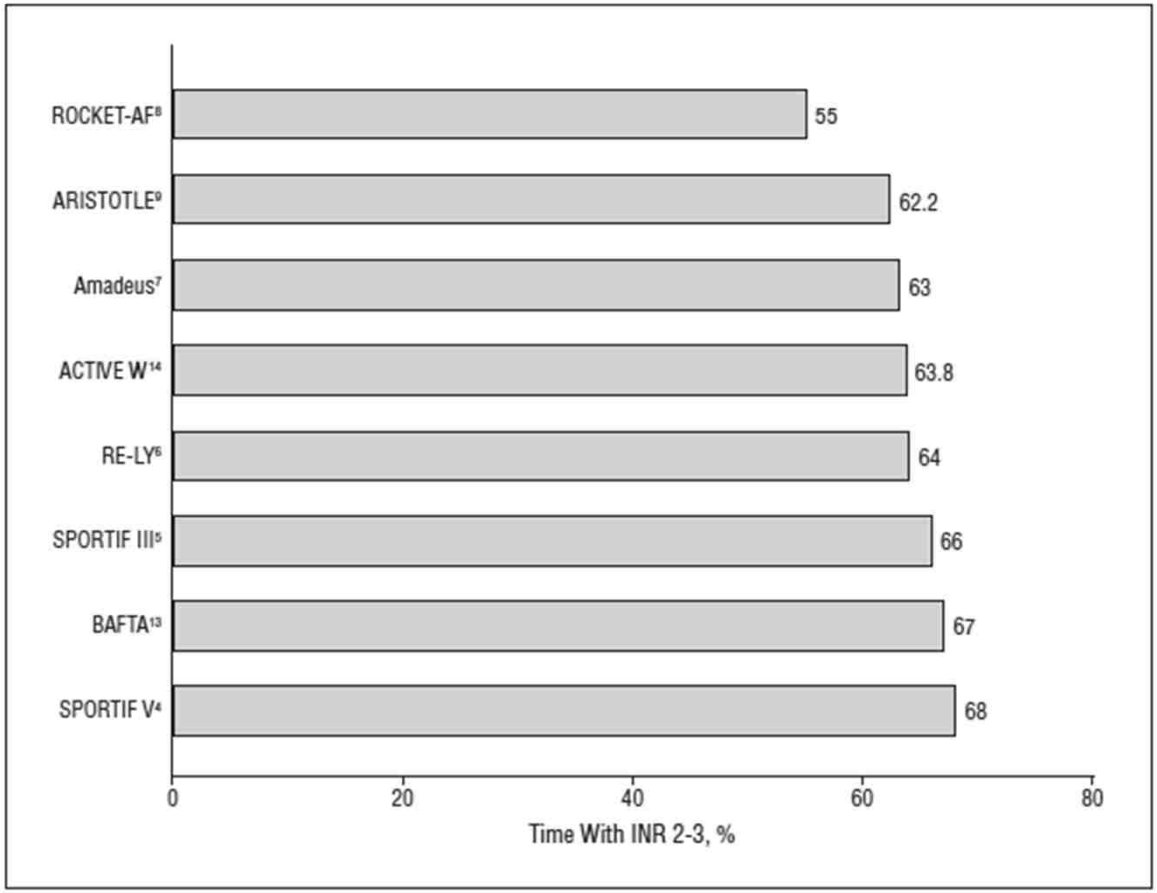


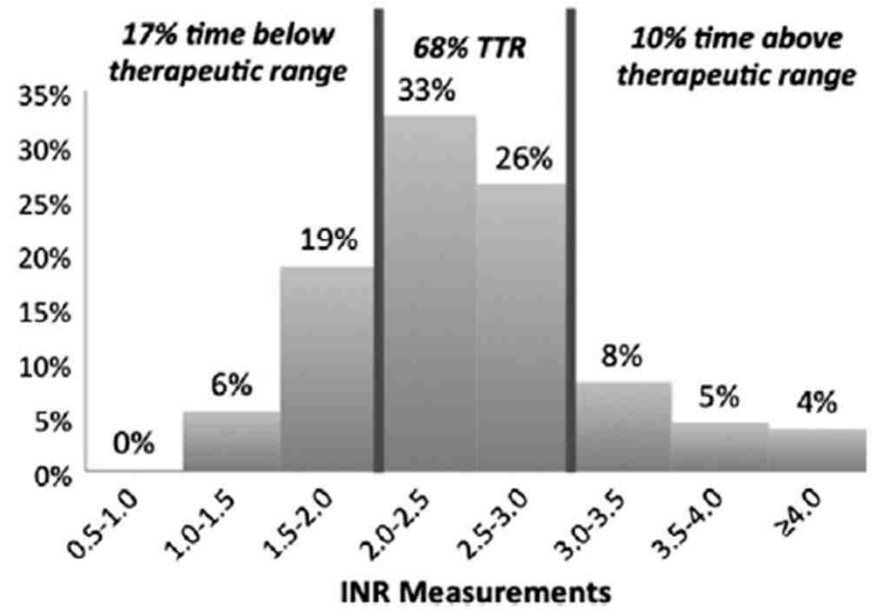
Figure 2. Bar graph demonstrating the proportion of time spent in therapeutic anticoagulation across the included studies. INR indicates international normalized ratio. See the "Results" section for expansions of the study names.

Arch Intern Med. 2012;172(8):623-631

Patients' time in therapeutic range on warfarin among US patients with atrial fibrillation: Results from ORBIT-AF registry

Sean D. Pokorney, MD, MBA,[a,b] DaJuanicia N. Simon, MS,[b] Laine Thomas, PhD,[b] Gregg C. Fonarow, MD,[c]

Figure 1



Distribution of INR measurements with median TTR and median time above/below therapeutic range displayed.

http://dx.doi.org/10.1016/j.ahj.2015.03.017

of Atrial Fibrillation (ORBIT-AF) is a US national prospective registry of AF.[12] Enrolling providers include primary

Am Heart J 2015;170:141-148.e1

ORIGINAL RESEARCH

American Heart Association | American Stroke Association

Relationship Between Time in Therapeutic Range and Comparative Treatment Effect of Rivaroxaban and Warfarin: Results From the ROCKET AF Trial

Jonathan P. Piccini, MD, MHS; Anne S. Hellkamp, MS; Yuliya Lokhnygina, PhD; Manesh R. Patel, MD; Frank E. Harrell, Jr, PhD; Daniel E. Singer, MD; Richard C. Becker, MD; Günter Breithardt, MD; Jonathan L. Halperin, MD; Graeme J. Hankey, MD; Scott D. Berkowitz, MD; Christopher C. Nessel, MD; Kenneth W. Mahaffey, MD; Keith A. A. Fox, MB, ChB; Robert M. Califf, MD; on behalf of the ROCKET AF Investigators*

Table 3. Stroke and Non-CNS Embolism by Quartiles of cTTR

	Rivaroxaban (N=6891)		Warfarin (N=7080)		Rivaroxaban vs Warfarin	
Center TTR	n/J (%)	Event Rate (100 Pt-Years)	n/J (%)	Event Rate (100 Pt-Years)	HR (95% CI)	Interaction *P* Value*
0.00% to 50.6%	45/1735 (2.6)	1.8	62/1689 (3.7)	2.5	0.70 (0.47, 1.04)	0.709
50.7% to 58.5%	53/1746 (3.0)	1.9	63/1807 (3.5)	2.2	0.90 (0.64, 1.26)	
58.6% to 65.7%	54/1734 (3.1)	1.9	62/1758 (3.5)	2.1	0.88 (0.62, 1.25)	
65.7% to 100.0%	37/1676 (2.2)	1.3	55/1826 (3.0)	1.8	0.73 (0.50, 1.06)	

The population for this analysis was the safety on-treatment population from sites with calculable cTTR. cTTR was calculated from all ITT warfarin patients at each center. All analyses are based on the time to first event. Event rates are the number of events per 100 patient-years of follow-up. HRs (95% CIs) are derived from a proportional hazards model with treatment as a covariate. CNS indicates central nervous system; cTTR, center-level time in therapeutic range; J, number of subjects in each subgroup; n, number of subjects with events.
*The *P* value for the interaction of treatment group and center-based INR control group based on the Cox proportional hazard model including treatment group, center-based INR control group, and their interaction.

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Received November 21, 2013; accepted February 19, 2014.

J Am Heart Assoc. 2014;3:e000521

ORIGINAL RESEARCH

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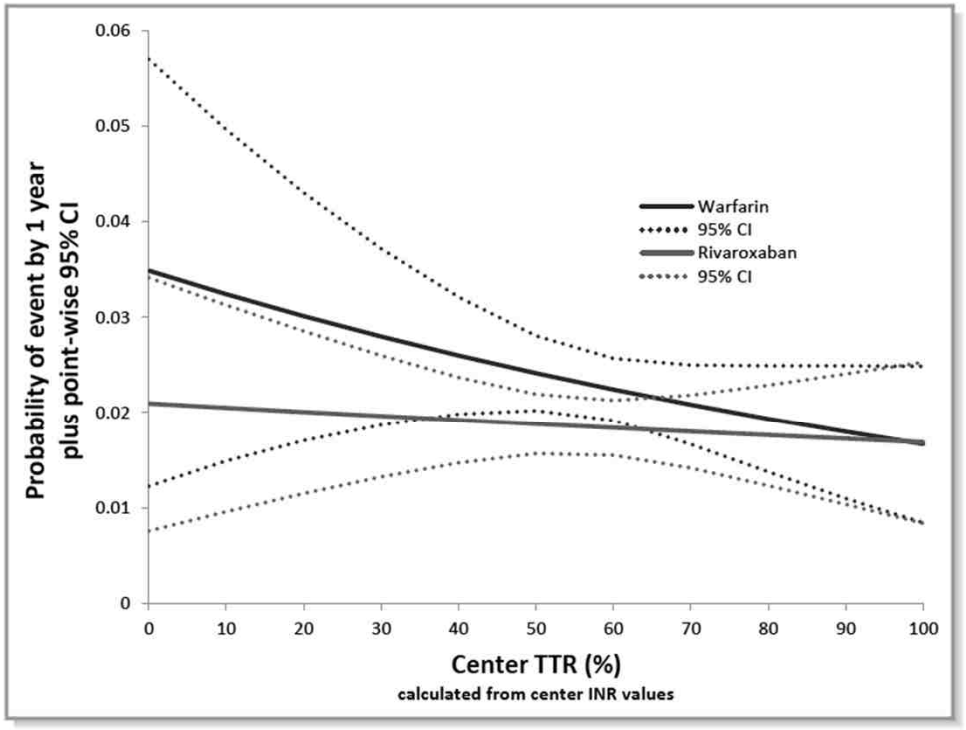

Figure 2. Probability of stroke or non-CNS embolism in rivaroxaban and warfarin treated patients according to cTTR. cTTR is shown on the *x*-axis. Probability of stroke or non-CNS embolism by 1-year of follow-up is shown on the *y*-axis. This plot shows the probability of having a stroke or non-CNS embolism according to cTTR for rivaroxaban- and warfarin-treated patients (solid lines) with corresponding 95% CIs (dashed lines). Centers with higher cTTR values had a lower risk of stroke and systemic embolus in both the rivaroxaban- and warfarin-treated arms. CNS indicates central nervous system; cTTR, center time in therapeutic range; INR, international normalized ratio.

Coumadin or NOAC?

Europace (2016) 18, 1609–1678

ESC GUIDELINES

Recommendations for stroke prevention in patients with atrial fibrillation

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Oral anticoagulation therapy to prevent thromboembolism should be considered in male AF patients with a CHA_2DS_2-VASc score of 1, considering individual characteristics and patient preferences.	IIa	B	371, 375–377
Oral anticoagulation therapy to prevent thromboembolism should be considered in female AF patients with a CHA_2DS_2-VASc score of 2, considering individual characteristics and patient preferences.	IIa	B	371, 376, 377
Vitamin K antagonist therapy (INR 2.0–3.0 or higher) is recommended for stroke prevention in AF patients with moderate-to-severe mitral stenosis or mechanical heart valves.	I	B	274, 435–440
When oral anticoagulation is initiated in a patient with AF who is eligible for a NOAC (apixaban, dabigatran, edoxaban, or rivaroxaban), a NOAC is recommended in preference to a vitamin K antagonist.	I	A	39, 318–321, 404
When patients are treated with a vitamin K antagonist, time in therapeutic range (TTR) should be kept as high as possible and closely monitored.	I	A	395, 432, 441-444
AF patients already on treatment with a vitamin K antagonist may be considered for NOAC treatment if TTR is not well controlled despite good adherence, or if patient preference without contra-indications to NOAC (e.g. prosthetic valve).	IIb	A	39, 318, 319, 404, 408
Combinations of oral anticoagulants and platelet inhibitors increase bleeding risk and should be avoided in AF patients without another indication for platelet inhibition.	III (harm)	B	429, 445
In male or female AF patients without additional stroke risk factors, anticoagulant or antiplatelet therapy is not recommended for stroke prevention.	III (harm)	B	368, 371, 376, 377
Antiplatelet monotherapy is not recommended for stroke prevention in AF patients, regardless of stroke risk.	III (harm)	A	38, 429, 430
NOACs (apixaban, dabigatran, edoxaban, and rivaroxaban) are not recommended in patients with mechanical heart valves (Level of evidence B) or moderate-to-severe mitral stenosis (Level of evidence C).	III (harm)	B C	318–321, 400, 404

Europace (Nov 2016) 18, 1609–1678

NOACs-Dosing Considerations

Europace (2015) 17, 514–523
doi:10.1093/europace/euu311

REVIEW

Non-vitamin K antagonist oral anticoagulants: considerations on once- vs. twice-daily regimens and their potential impact on medication adherence

Table 2 Non-VKA oral anticoagulant drugs, approved for prevention of systemic embolism or stroke in patients with non-valvular AF

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Action	Direct thrombin inhibitor	Activated factor Xa inhibitor	Activated factor Xa inhibitor	Activated factor Xa inhibitor
Dose	150 mg BID 110 mg BID[a,b] (75 mg BID)[b]	5 mg BID 2.5 mg BID[a]	60 mg OD[c] 30 mg OD[a]	20 mg OD 15 mg OD[a]
Phase III clinical trial	RE-LY[25]	ARISTOTLE[26] AVERROES[27]	ENGAGE-AF[28]	ROCKET-AF[29]

BID, twice a day; OD, once daily.
[a]See further tables and text for discussion on dose reduction considerations.
[b]110 mg BID not approved by FDA. 75 mg BID approved in USA only, if CrCl 15–30 mL/min or if CrCl 30–49 mL/min and other 'orange' factor as in *Table 6* (e.g. verapamil).
[c]FDA provided a boxed warning that 'edoxaban should not be used in patients with CrCL > 95 mL/min'. EMA advised that 'edoxaban should only be used in patients with high creatinine clearance after a careful evaluation of the individual thrombo-embolic and bleeding risk'.

Later, the term 'patient compliance' has been increasingly replaced by 'medication adherence'. The shift from 'compliance' to 'adherence' reflects a fundamental change in understanding relationships

Still, the decision to discontinue anticoagulation therapy after a major bleed will likely be the result of a joint decision from the patient and physician, although patient views may temper the final decision on

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Europace (2015) 17, 514–523

NOACs-Dosing Considerations

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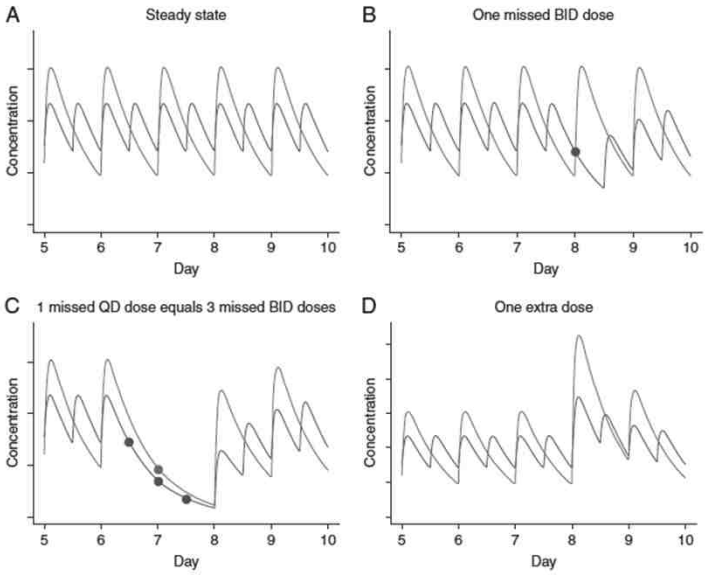


Figure 2 Once-daily vs. twice-daily dosing: difference between intake and predicted biological impact in general. Different patterns of non-adherence lead to different exposition to 'risk' between once-daily and twice-daily drugs. These graphs illustrate the theoretical pharmacokinetic profiles of a dose X administered once-daily (QD), and a dose X/2 administered twice-daily (BID), for a drug with a half-life of about 12 h and a T_{max} of 3 h. (*A*) the peak-to-trough ratio is much smaller for the BID than the QD dosing. (*B*) The concentration after a single missed BID dose (red dot) is similar to the expected trough concentration of QD dosing, suggesting that missing a single dose of a twice-daily dosing regimen should not be therapeutically critical. (*C*) The pharmacological equivalent of missing a single dose in a once-daily regimen (blue dot) is missing three consecutive doses (red dots) of a twice-daily dosing regimen. (*D*) Taking an extra dose results in a much higher peak for the QD than for the BID dosing regimen.

Europace (2015) 17, 514–523

Bottom Line Recommendation

- **For patients *on* Warfarin who have "bullet proof" INRs (> 70% TTR), continue with Coumadin with the policy that should they begin to fall out of range, switch to a NOAC**
- **For new starts (recently diagnosed atrial fibrillation), it's probably best to start a NOAC in the absence of severe renal disease (eGRF < 15 ml/min)**
- **Consider a bid dosing NOAC—Apixiban or Dabigatran**

Prevention of Thromboembolic Complications in Atrial Fibrillation (Ten things to consider)

- **You must know the** CHA_2DS_2-VASc score
- What does the term “non valvular atrial fibrillation mean”?
- “Congestive heart failure” includes patients with normal EF
- Hypertension includes “treated hypertension”
- At what point do I start anticoagulation?
- What about aspirin for stroke prevention?
- Coumadin or NOAC? – “Time in Therapeutic Range” and Dosing considerations
- *Which NOAC is best?*

Which NOAC is best?

AHA/ACC/HRS Practice Guideline

2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation

A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society

Developed in Collaboration With the Society of Thoracic Surgeons

4. Prevention of Thromboembolism

4.1. Risk-Based Antithrombotic Therapy: Recommendations

See Table 6 for a summary of recommendations from this section.

Class I

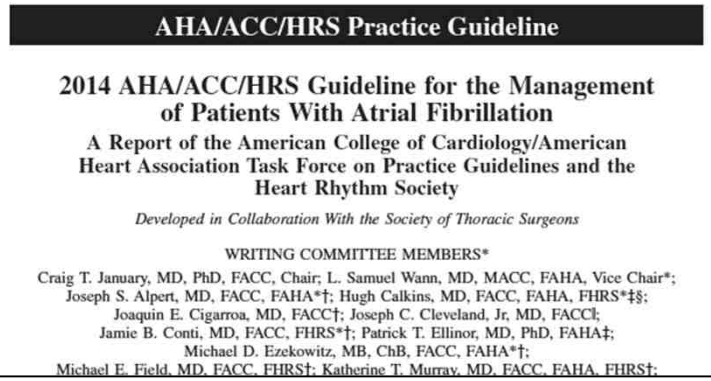
1. **In patients with AF, antithrombotic therapy should be individualized based on shared decision making after discussion of the absolute risks and RRs of stroke and bleeding and the patient's values and preferences.** ***(Level of Evidence: C)***

(*Circulation*. 2014;130:e199-e267.)

Circulation is available at http://circ.ahajournals.org DOI: 10.1161/CIR.0000000000000041

Circulation 2014;130:e199-e267

Which NOAC is best?



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A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society

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"***Missing even 1 dose of a NOAC*** could result in a period without protection from thromboembolism. As a result, the ***FDA issued black box warnings that discontinuation of these new agents can increase the risk of thromboembolism*** and that coverage with another anticoagulant may be needed."

entities may apply; see Appendix 1 for recusal information.

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This document was approved by the American College of Cardiology Board of Trustees, the American Heart Association Science Advisory and Coordinating Committee, and the Heart Rhythm Society Board of Trustees in March 2014.

The online-only Comprehensive Relationships Data Supplement is available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000041/-/DC1.

The online-only Data Supplement files are available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIR.0000000000000041/-/DC2.

The American Heart Association requests that this document be cited as follows: January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *Circulation* 2014;130:e199–e267.

This article is copublished in the *Journal of the American College of Cardiology*.

Copies: This document is available on the World Wide Web sites of the American Heart Association (my.americanheart.org), the American College of Cardiology (www.cardiosource.org), and the Heart Rhythm Society (www.hrsonline.org). A copy of the document is available at http://my.americanheart.org/statements by selecting either the "By Topic" link or the "By Publication Date" link. To purchase additional reprints, call 843-216-2533 or e-mail kelle.ramsay@wolterskluwer.com.

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NOACs-Dosing Considerations

Europace (2015) 17, 514–523
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REVIEW

Non-vitamin K antagonist oral anticoagulants: considerations on once- vs. twice-daily regimens and their potential impact on medication

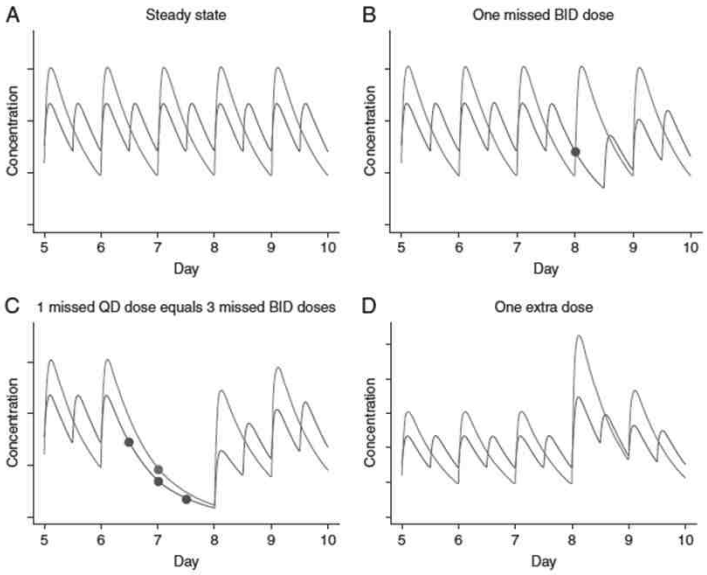

Figure 2 Once-daily vs. twice-daily dosing: difference between intake and predicted biological impact in general. Different patterns of non-adherence lead to different exposition to 'risk' between once-daily and twice-daily drugs. These graphs illustrate the theoretical pharmacokinetic profiles of a dose X administered once-daily (QD), and a dose X/2 administered twice-daily (BID), for a drug with a half-life of about 12 h and a T_{max} of 3 h. (*A*) the peak-to-trough ratio is much smaller for the BID than the QD dosing. (*B*) The concentration after a single missed BID dose (red dot) is similar to the expected trough concentration of QD dosing, suggesting that missing a single dose of a twice-daily dosing regimen should not be therapeutically critical. (*C*) The pharmacological equivalent of missing a single dose in a once-daily regimen (blue dot) is missing three consecutive doses (red dots) of a twice-daily dosing regimen. (*D*) Taking an extra dose results in a much higher peak for the QD than for the BID dosing regimen.

Europace (2015) 17, 514–523

Which NOAC is best?

EBioMedicine 4 (2016) 26–39

Table 4
Suggested patient groups in which specific non-VKA oral anticoagulants (NOACs) may be relatively advantageous.

Individual patient groups and characteristics		NOACs with characteristics beneficial to target group
Elderly patients	Consider comorbidities and agents with lower extracranial haemorrhage among elderly (age > 75)	Apixaban Edoxaban
Renal impairment (45 ml/min > CrCl > 15 ml/min)	Consider agents with lower haemorrhagic complications in moderate to severe renal impairment	Apixaban
Previous GI haemorrhage	Consider agents with no increased risk of GI haemorrhage	Apixaban Dabigatran 110 mg
High bleeding risk (HAS-BLED ≥ 3)	Consider agents with lower incidence of extracranial haemorrhage	Apixaban Dabigatran 110 mg Edoxaban
Recurrent stroke despite well managed VKA	Consider agent with demonstrable benefit in reducing both ischaemic AND haemorrhagic stroke	Dabigatran 150 mg
Preference for low pill burden	Consider once daily formulations	Edoxaban Rivaroxaban

Abbreviations: CrCl creatinine clearance, HAS-BLED: H, hypertension, A, abnormal renal and liver function, S, stroke, B, bleeding tendency, L, labile INRs, E, elderly, D, drugs. GI gastrointestinal, VKA vitamin K antagonist.

http://dx.doi.org/10.1016/j.ebiom.2015.07.017

EBioMedicine 4 (2016) 26–39

Which NOAC is best?

ORIGINAL RESEARCH

American Heart Association | American Stroke Association

Effectiveness and Safety of Dabigatran, Rivaroxaban, and Apixaban Versus Warfarin in Nonvalvular Atrial Fibrillation

Xiaoxi Yao, PhD; Neena S. Abraham, MD, MSCE; Lindsey R. Sangaralingham, MPH; M. Fernanda Bellolio, MD, MS; Robert D. McBane, MD; Nilay D. Shah, PhD; Peter A. Noseworthy, MD

Background—The introduction of non–vitamin K antagonist oral anticoagulants has been a major advance for stroke prevention in atrial fibrillation; however, outcomes achieved in clinical trials may not translate to routine practice. We aimed to evaluate the effectiveness and safety of dabigatran, rivaroxaban, and apixaban by comparing each agent with warfarin.

Methods and Results—Using a large US insurance database, we identified privately insured and Medicare Advantage patients with nonvalvular atrial fibrillation who were users of apixaban, dabigatran, rivaroxaban, or warfarin between October 1, 2010, and June 30, 2015. We created 3 matched cohorts using 1:1 propensity score matching: apixaban versus warfarin (n=15 390), dabigatran versus warfarin (n=28 614), and rivaroxaban versus warfarin (n=32 350). Using Cox proportional hazards regression, we found that for stroke or systemic embolism, apixaban was associated with lower risk (hazard ratio [HR] 0.67, 95% CI 0.46–0.98, *P*=0.04), but dabigatran and rivaroxaban were associated with a similar risk (dabigatran: HR 0.98, 95% CI 0.76–1.26, *P*=0.98; rivaroxaban:

Conclusions—In patients with nonvalvular atrial fibrillation, apixaban was associated with lower risks of both stroke and major bleeding, dabigatran was associated with similar risk of stroke but lower risk of major bleeding, and rivaroxaban was associated with similar risks of both stroke and major bleeding in comparison to warfarin. (*J Am Heart Assoc*. 2016;5:e003725 doi: 10.1161/JAHA.116.003725)

Atrial fibrillation (AF) is common, with a 1-in-4 lifetime risk after age 40 years,[1] and is associated with a 3- to 5-fold increased risk of stroke.[2,3] Treatment with warfarin can reduce the risk of stroke by 60% to 70%,[4] but its use can be cumbersome because of numerous food and drug interactions and the need for ongoing laboratory testing and dose adjustment.[5] Non–vitamin K antagonist oral anticoagulants (NOACs) provide more convenient therapeutic options and have demonstrated at least equivalent efficacy in comparison to warfarin in large phase III clinical trials.[6–9]

The efficacy and safety achieved in the idealized clinical trial settings may not necessarily translate to routine practice because of the differences in the patient populations, the intensity of follow-up, and the variations in care that patients receive. Extrapolating findings from trials to general practice is especially challenging for anticoagulation therapies. Because anticoagulants are long-term preventive medications that address no ongoing symptoms, adherence is substantially lower in observational studies than in clinical trials.[10–13] Furthermore, appropriate dosing may be hard to achieve in clinical practice because of the complexity of real-world settings.[14]

As these medications are more broadly adopted,[15,16] ongoing evaluation of their effectiveness and safety is important. Until observational studies confirm the generalizability of the clinical trials, some clinicians may remain skeptical and withhold NOACs from patients who stand to

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Received April 13, 2016; accepted May 13, 2016.

J Am Heart Assoc. 2016;5:e003725

Bottom line: Which NOAC is best?

- No head to head trials between NOACs
- Apixiban favored in current expert reviews and recent claims data base analysis

Prevention of Thromboembolic Complications in Atrial Fibrillation (Ten things to consider)

- **You must know the** CHA_2DS_2-VASc score
- What does the term “non valvular atrial fibrillation mean”?
- “Congestive heart failure” includes patients with normal EF
- Hypertension includes “treated hypertension”
- What about aspirin for stroke prevention?
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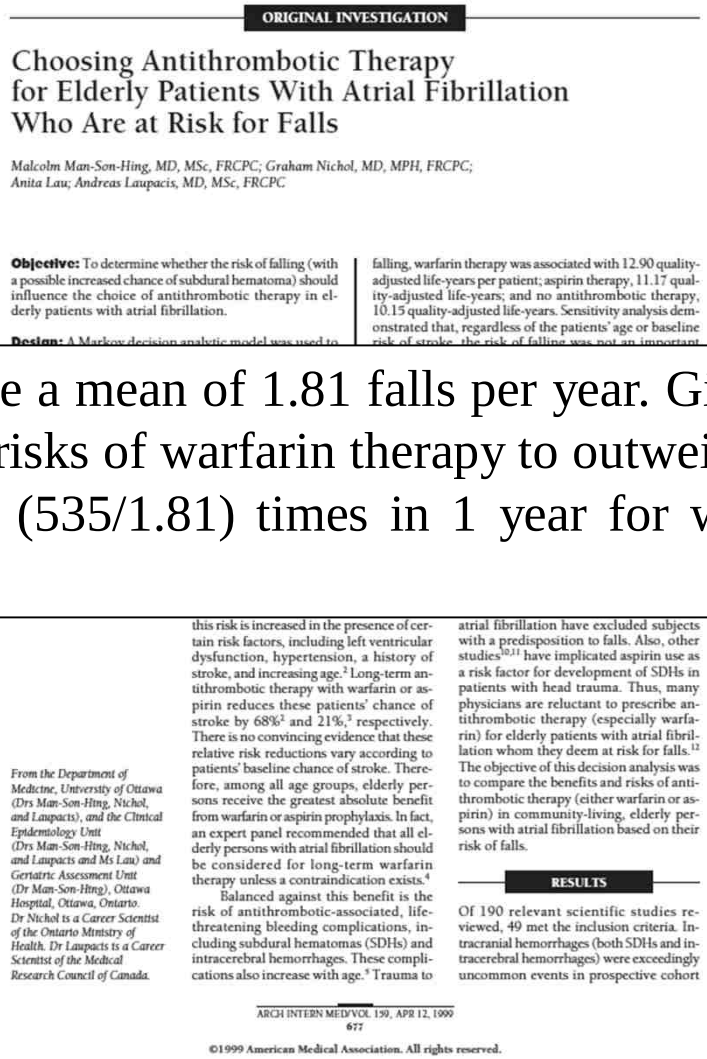
- Coumadin or NOAC? – “Time in Therapeutic Range”, dosing and posing considerations
- Which NOAC is best?
- *What about my elderly patient who falls a lot?*

What about my elderly patient who falls a lot?



ORIGINAL INVESTIGATION

Choosing Antithrombotic Therapy for Elderly Patients With Atrial Fibrillation Who Are at Risk for Falls

Malcolm Man-Son-Hing, MD, MSc, FRCPC; Graham Nichol, MD, MPH, FRCPC; Anita Lau; Andreas Laupacis, MD, MSc, FRCPC

Objective: To determine whether the risk of falling (with a possible increased chance of subdural hematoma) should influence the choice of antithrombotic therapy in elderly patients with atrial fibrillation.

falling, warfarin therapy was associated with 12.90 quality-adjusted life-years per patient; aspirin therapy, 11.17 quality-adjusted life-years; and no antithrombotic therapy, 10.15 quality-adjusted life-years. Sensitivity analysis demonstrated that, regardless of the patients' age or baseline

"Elderly persons who fall have a mean of 1.81 falls per year. Given that the risk of SDH must be 535-fold or greater for the risks of warfarin therapy to outweigh the benefits, persons taking warfarin must fall about 295 (535/1.81) times in 1 year for warfarin to not be the optimal therapy."

From the Department of Medicine, University of Ottawa (Drs Man-Son-Hing, Nichol, and Laupacis), and the Clinical Epidemiology Unit (Drs Man-Son-Hing, Nichol, and Laupacis and Ms Lau) and Geriatric Assessment Unit (Dr Man-Son-Hing), Ottawa Hospital, Ottawa, Ontario. Dr Nichol is a Career Scientist of the Ontario Ministry of Health. Dr Laupacis is a Career Scientist of the Medical Research Council of Canada.

this risk is increased in the presence of certain risk factors, including left ventricular dysfunction, hypertension, a history of stroke, and increasing age.[2] Long-term antithrombotic therapy with warfarin or aspirin reduces these patients' chance of stroke by 68%[2] and 21%,[3] respectively. There is no convincing evidence that these relative risk reductions vary according to patients' baseline chance of stroke. Therefore, among all age groups, elderly persons receive the greatest absolute benefit from warfarin or aspirin prophylaxis. In fact, an expert panel recommended that all elderly persons with atrial fibrillation should be considered for long-term warfarin therapy unless a contraindication exists.[4]

Balanced against this benefit is the risk of antithrombotic-associated, life-threatening bleeding complications, including subdural hematomas (SDHs) and intracerebral hemorrhages. These complications also increase with age.[5] Trauma to

atrial fibrillation have excluded subjects with a predisposition to falls. Also, other studies[10,11] have implicated aspirin use as a risk factor for development of SDHs in patients with head trauma. Thus, many physicians are reluctant to prescribe antithrombotic therapy (especially warfarin) for elderly patients with atrial fibrillation whom they deem at risk for falls.[12] The objective of this decision analysis was to compare the benefits and risks of antithrombotic therapy (either warfarin or aspirin) in community-living, elderly persons with atrial fibrillation based on their risk of falls.

RESULTS

Of 190 relevant scientific studies reviewed, 49 met the inclusion criteria. Intracranial hemorrhages (both SDHs and intracerebral hemorrhages) were exceedingly uncommon events in prospective cohort

ARCH INTERN MED/VOL 159, APR 12, 1999

What about my elderly patient who falls a lot?

CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

Risk of Falls and Major Bleeds in Patients on Oral Anticoagulation Therapy

Jacques Donzé, MD, MSc,[a] Carole Clair, MSc, MD,[b] Balthasar Hug, MD, MBA, MPH,[c] Nicolas Rodondi, MD, MAS,[d] Gérard Waeber, MD,[e] Jacques Cornuz, MD, MPH,[b] Drahomir Aujesky, MD, MSc[d]

[a]Division of General Internal Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Mass; [b]Department of Ambulatory Care and Community Medicine, University Hospital of Lausanne, Lausanne, Switzerland; [c]Division of General Internal Medicine, University Hospital of Basel, Basel, Switzerland; [d]Division of General Internal Medicine, Bern University Hospital, Bern, Switzerland; [e]Division of General Internal Medicine, University Hospital of Lausanne, Lausanne, Switzerland.

"Of 515 enrolled patients on OACs, 308 patients (59.8%) were at high risk of falls... In multivariate analysis, ***a high falls risk was not statistically significantly associated with the risk of a major bleed.***"

"CONCLUSIONS: In this prospective cohort, ***patients on oral anticoagulants at high risk of falls did not have a significantly increased risk of major bleeds. These findings suggest that being at risk of falls is not a valid reason to avoid oral anticoagulants in medical patients."***

Funding: This study was financially supported by an intramural grant (CardioMet) from the University Hospital Lausanne, Switzerland and the Swiss Science National Foundation (PBLAP3-131814).

Conflict of Interest: None.

Authorship: All authors had access to the data and had a role in writing the manuscript.

Requests for reprints should be addressed to Jacques Donzé, MD, Division of General Internal Medicine, Brigham and Women's Hospital, 1620 Tremont Street, OBC-3-2U, Boston, MA 02120-1613.

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http://dx.doi.org/10.1016/j.amjmed.2012.01.033

populations such as inpatients or those with atrial fibrillation, and are based on falls risks as assessed by physician reports or International Classification of Diseases, 9th Revision, Clinical Modification codes.[7-10] Moreover, patients at high risk of falls are themselves often excluded from clinical anticoagulation trials.[11] Our aim was to prospectively evaluate whether medical patients on oral anticoagulants who are considered at high risk of falls based on 2 validated questions have an increased risk of major bleeds compared with patients at low risk of falls.

ARCH INTERN MED/VOL 163, JULY 14, 2003

Bottom line: What about my elderly patient who falls a lot?

- The risks of serious injury while on OAC is likely over-estimated resulting in under prescription of medicines that have been clearly shown to reduce stroke/TE.
- Prescribe OACs for your elderly patients with afib—even those at risk for falls

ARCH INTERN MED/VOL 163, JULY 14, 2003

Prevention of Thromboembolic Complications in Atrial Fibrillation (Ten things to consider)

- **You must know the** CHA_2DS_2-VASc score
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- “Congestive heart failure” includes patients with normal EF
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- Which NOAC is best?
- What about my elderly patient who falls a lot?
- *What about brief and or “silent” episodes of atrial fibrillation?*

The problem of brief afib

- “Selection of antithrombotic therapy should be based on the risk of thromboembolism irrespective of whether the AF pattern is paroxysmal, persistent, or permanent.” (HRS/ACC/AHA Guidelines 2014)
- “By accepted convention, an episode lasting at least 30 seconds is diagnostic.” (ESC Afib Guidelines 2016)
- Clinical scenario: 76 yo female with HTN is referred to you for evaluation of syncope. A Holter is ordered and on it, you find 1.3 min of atrial fibrillation during which the patient is asymptomatic

Thank you

Questions and Answers